Individual differences in synaesthesia

Qualitative and fMRI investigations on the impact of synaesthetic phenomenology

Cassandra Gould

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Declaration

I hereby declare that this thesis has not been and will not be submitted in whole or in part to another University for the award of any other degree.

Signature:

Cassandra Gould

UNIVERSITY OF SUSSEX

Cassandra Gould, Doctor of Philosophy

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Summary

Synaesthesia is a cognitive trait in which stimuli of one sensory modality are automatically and consistently experienced in conjunction with perceptions in a separate modality or processing stream. Investigations of synaesthesia may help determine the neural processing required in the generation of a conscious experience. In order to gain the most complete understanding of synaesthesia, we have applied an integrated neurophenomenological approach.

In Chapter 2 we present an extended case study of spatial-form synaesthesia (SFS) phenomenology. This investigation goes significantly beyond the rudimentary accounts of provided elsewhere, and provides novel observations on inducer-concurrent relationships, suggesting that guided introspection techniques can provide neurobehaviourally relevant information.

In Chapters 3-5 we investigate neural activity in grapheme-colour synaesthesia (GCS). In Chapter 3 we demonstrate that activation in colour selective areas during synaesthetic colour processing is dependent on individual differences in phenomenology, thereby reconciling previous attempts to replicate this key finding in the GCS literature. In Chapter 4 we find no evidence for trait level differences in context specific functional connectivity in GCS, however, we demonstrate that localisation of the synaesthetic concurrents modulate connectivity between colour and low-level visual areas. In 5 we replicate findings of trait level differences in resting state fronto-parietal networks, suggesting that the RFPN may be a significant network in aspects of the synaesthetic experience common to all participants. We demonstrate that localisation of concurrents also modulates resting state visual networks, whilst automaticity of concurrents modulates parietal networks. Both Chapters 4 and 5 support a model of synaesthesia in which localisation of concurrents is modulated by bottom-up connectivity, between colour and early visual areas.

This thesis demonstrates that individual differences in synaesthetic phenomenology significantly impact neural activity. We propose that future investigations place emphasis on the phenomenological experience of the participant in the interpretation of neural effects.

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Table 1: List of abbreviations (continued over).

Abbreviation	Meaning
AAL	Automated Anatomical Labelling
ACC	Anterior Cingulate Cortex
AIP	Anterior Interparietal Sulcus
AN	Auditory Network
ANOVA	Analysis of Variance
BOLD	Blood Oxygen Level Dependant
CIELUV	International Commission on Illumination (CIE) Adams chromatic valence (L*, u*, v*) colour space
CIP	Caudal Interparietal Sulcus
CLaN	Coloured Letters and Numbers questionnaire
CLaN-A	Coloured Letters and Numbers questionnaire - Automaticity
CLaN-L	Coloured Letters and Numbers questionnaire - Localisation
cMond	Coloured Mondrian
DCM	Dynamic Causal Modelling
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
EC	Effective Connectivity
ECN	Executive control network
EEG	Electroencephalography
EI	Elicitation Interview, also known as Explicitation Interview
EPI	Echo-Planer Imaging
FA	Fractional Anisotropy
FC	Functional Connectivity
FG	Fusiform Gyrus
FMH	Farnsworth-Munsell Hue test

Table 2: List of abbreviations (continued).

Abbreviation	Meaning
fMRI	Functional Magnetic Resonance Imaging
FWE	Family Wise Error
FWHM	Full Width at Half Maximum
GCS	Grapheme-Colour Synaesthesia
GIFT	Group ICA for fMRI Toolbox
GLM	General Linear Model
GM	Grey Matter
gMond	Greyscale Mondrian
GT	Grounded Theory
HRF	Haemodynamic Response Function
IC	Independent Components
ICA	Independent Components Analysis
ICN	Intrinsic Connectivity Network
ISEQ	Illustrated Synaesthesia Experience Questionnaire
KS	Kolmogorov-Smirnov
Lb	Black Letters
LFPN	Left Fronto-parietal Network
LSA	Letter Shape Area
LVN	Lateral Visual Network
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MVN	Medial Visual Network
OperRIFG	Opercular part of Right Inferior Frontal Gyrus
PA	Projector-Associator
PPI	Psychophysical Interactions

Table 3: List of abbreviations (continued).

Abbreviation	Meaning
pSTG	Posterior Superior Temporal Gyrus
ReML	Restricted Maximum Likelihood
RFPN	Right Fronto-parietal Network
RGB	Red, Green, Blue
ROI	Region of Interest
rsFC	Resting State Functional Connectivity
rs-fMRI	Resting State Functional Magnetic Resonance Imaging
RS-PA	Rouw and Scholte Projector-Associator questionnaire
sb	Black Symbols
SEM	Structural Equation Modelling
SFS	Spatial Form Synaesthesia, also known as Sequence Space Synaesthesia
SMN	Sensory motor network
SNARC	Spatial Numerical Association of Response Codes
SPL	Superior Parietal Lobe
SPM	Statistical Parametric Mapping
SPVN	Striate and polar visual network
T1	Spin lattice relaxation time
TE	Echo Time
TPN	Temporo-parietal Network
TR	Repetition Time
V1	Visual area 1
V2	Visual area 2
V4	Visual area 4
VBM	Voxel Based Morphometry
VIF	Variance Inflation Factor
VWFA	Visual Word Form Area

Chapter 1

Introduction

The generation of a conscious percept is believed to be results of a combination of external input and neural modulation of that input. In most populations, different individuals show a high degree of agreement in the descriptions of conscious experience resultant of a given input. In certain clinical and non-clinical populations, however, the description of an experience can vary widely in its basic phenomenological features. This variation may simply be a matter of semantics - what I call "terracotta", you may call "burnt orange" - however, in other cases, differences in description may suggest that our conscious phenomenological experiences are intrinsically different. In this thesis we investigate synaesthesia: a cognitive trait in which stimulation of one processing stream leads to a conscious phenomenological experience generated by different neural processing stream or modality. The phenomenological descriptions provided by a person with synaesthesia reflect not only the external input, but for certain sets of stimuli they also suggest activity in a linked processing stream. In this thesis we investigate synaesthesia through both qualitative and fMRI methods, in order to shed light on the processes involved in the generation of the conscious synaesthetic experience. We do so with particular regard for the role of individual differences in the phenomenological experience and an exploration of suitable methods for gaining detailed first-person phenomenological reports of experience. With the assumption that variation in phenomenology reflects variation in neurology, we investigate the impact of individual differences in phenomenology on neural data. These investigations contribute to synaesthesia, and consciousness research more widely, by exemplifying the approach of 'neurophenomenology' (Varela, 1996) in addressing the hard problem of consciousness (Rudrauf, Lutz, Cosmelli, Lachaux, & Le Van Quyen, 2003).

1.1 Synaesthesia

Synaesthesia is a cognitive trait in which stimuli of one sensory modality are automatically and consistently experienced in conjunction with perceptions in a separate modality or processing stream. The trigger for synaesthetic percepts is known as the 'inducer' and the synaesthetic percept itself is known as the 'concurrent'. Synaesthesia characterises a group of experiences in which two perceptual features are 'joined'. Examples of the trait include auditory-colour synaesthesia, in which specific combinations of colour and motion are perceived in response to auditory stimuli (Cytowic, 1989) and lexical-gustatory synaesthesia, in which the auditory or visual presentation of words is associated with sensations of tastes (Ferrari, 1907; Pierce, 1907). The study of synaesthesia is relevant to the study of consciousness as synaesthetes have a conscious experience (concurrent) which

is not directly attributable to the external stimulus, i.e. although an inducing item (e.g. a sound) is present in the external environment, the concurrent percept (e.g. a colour) is not. Investigations which can shed light on the processes involved in the generation of a synaesthetic concurrent may therefore open a window into the formation of other conscious experience.

Synaesthetes do not show an increased incidence of psychiatric or neurological disorders, but they have been shown to exhibit perceptual and behavioural advantages over non-synaesthetes in the concurrent processing modality (Banissy, Walsh, & Ward, 2009; Ward, Jonas, Dienes, & Seth, 2010). Synaesthesia therefore provides a unique opportunity to study altered conscious states in a population which are on the whole free from significant clinical disorders; as synaesthetes are otherwise healthy we may expect any differences in neurological or behavioural data to be free from some of the more complex interactions which may be found in clinical psychiatric disorders of consciousness.

In this thesis we investigate two forms of synaesthesia: i) spatial-form synaesthesia (SFS), in which ordinal sequences induce spatial reference frames; ii) grapheme-colour synaesthesia (GCS), in which letters and numbers induce an experience of colour. SFS and GCS are two of the most widely studied forms of synaesthesia (Price & Mattingley, 2012), not only due to their high incidence (1.4% (Banissy, Cohen Kadosh, Maus, Walsh, & Ward, 2009) and up to 20% (Mann, Korzenko, Carriere, & Dixon, 2009; Sagiv, Simner, Collins, Butterworth, & Ward, 2006) respectively), but also because they lend themselves to experimental manipulation and control of inducer presentation (compare this with music-colour synaesthesia, where the perceptual qualities of the inducer may be more idiosyncratic and less well characterised). In exploring SFS and GCS, we demonstrate that it is possible to gain considerable depth in first-person reports of the phenomenological experience of synaesthesia, and we suggest a number of avenues for the treatment and use of such data. We also use recently developed questionnaire measures of first-person synaesthetic phenomenology (Rothen, Tsakanikos, et al., 2013) to model the impact of individual differences in neural data.

1.1.1 Spatial-form synaesthesia

In spatial-form synaesthesia, ordinal sequences such as numbers, the alphabet, and days of the week lead to the concurrent percept of a spatial location (Price, 2009; Simner, Mayo, & Spiller, n.d.). The concurrent spatial location can be experienced as an externalised reference frame (i.e. with a location external to the synaesthete, in peripersonal space)

or it can be experienced as an association to a location (Ward, 2013). The concurrent spatial percept in SFS has been shown to trigger shifts of attention to that location, in a manner similar to directional instructions (Diesendruck et al., 2010). Each 'sub-type' of SFS is defined by the inducer set, for example where inducers are numbers, the concurrent is known as a 'number form', equally calendar items induce a 'calendar form'. It has been suggested that each of these different forms may be associated with distinct behavioural correlates (Price & Mattingley, 2012), implying that each may be supported by distinct neural mechanisms.

Previous research interest in SFS have primarily focused on confirming the perceptual nature of this trait. Most commonly, participants are required to produce a graphical or descriptive representation of their SFS on a number of occasions, with 'genuineness' of the trait validated by consistency in this representation in test/re-test (Sagiv et al., 2006). Other investigations have sought to characterise the trait in terms of behavioural differences; SFS has been demonstrated to confer improved behavioural performance compared to controls in a number of domains, including visuospatial working memory, visuospatial imagery, sequence representation and memory for personal or historical dates (see Price and Mattingley (2012) for a review). Neural investigations of SFS have suggested that the generation of the synaesthetic form in SFS requires integration between structures which confer the representation of ordinal sequences, e.g. the right lateralised ventral visual stream (Eagleman, 2009), and a separate structure or network which specifies the spatial relationship between the individual and the synaesthetic concurrent (Ward, 2013), e.g. the interparietal sulcus (Tang, Ward, & Butterworth, 2008). Price and Mattingley (2012) have argued that SFS does not result from specific neural abnormalities in these regions, rather it may result from simple rehearsal mechanisms.

Despite its commonality, our understanding of the phenomenological experience of SFS is generally limited to the reproduction of schematic spatial representations of concurrents (see for example Figure 2.1). We propose that obtaining more detailed information regarding the phenomenological experience of SFS is beneficial to research efforts, as first-person reports may inspire new research directions and provide a window into the cognitive architecture of concurrent generation.

1.1.2 Grapheme-colour synaesthesia

Grapheme-colour synaesthesia involves graphemic inducers (letters or numbers) and the automatic experience of associated colour concurrents. The specific nature if the colour

experience is known to vary within the population, not only in terms of the precise inducer-concurrent pairings, but also in the spatial location which the subject reports the colour to exist. the terms 'projector' and 'associator' were coined by Smilek and Dixon (2002) and Dixon, Smilek, and Merikle (2004) to describe the location of the concurrent as either external to the subjects peripersonal space (projector synaesthetes) or as a distinct feeling of knowing what colour is associated with the letter but no external percept (associator synaesthetes). This distinction has recently been developed to include a novel category of 'mental screen projectors' (van Leeuwen, den Ouden, & Hagoort, 2011), who report to *see* a colour (rather than simply *know* what the colour is), but they do not see it with an external location.

As with SFS, early research efforts in GCS focused on providing behavioural or neural validation of the subjective reports. More recently however, there has been a move to understand the neural activity which is responsible to the expression of the trait. In performing these investigations, it has been recognised that individual variability in features such as the projector-associator dimension may be the result of distinct and dissociable mechanisms, thus we should seek to understand the distinctions between the projector-like and associator-like experiences, and determine if they are indeed dissociable. Such knowledge may be effectively achieved by obtaining precise and relevant information on the first-person phenomenological experience of GCS.

GCS has been demonstrated to confer a performance advantage in tasks which engage the concurrent processing modality. It has been demonstrated that grapheme-colour synaesthetes exhibit increased acuity in veridical (i.e. externally presented) colour discrimination, evident in significantly improved performance over controls in the Fansworth-Munsell Hue (FMH) test (Banissy, Cohen Kadosh, et al., 2009; Yaro & Ward, 2007). The FMH test requires subjects to arrange 85 items into a sequence of consistently varying colour (Farnsworth. D, 1957) and thus requires perceptual decision making based on discrimination of slight changes in hue. The observation that grapheme-colour synaesthetes are able to perform this discrimination task, with a significantly improved level of accuracy over controls, suggests that there may be a specific difference in hue detection processes in GCS. Processing of veridical colour information has been characterised as occurring over a distributed network of areas in control populations (Gegenfurtner, 2003), including V1 and V2 (S. Engel, Zhang, & Wandell, 1997; S. A. Engel & Furmanski, 2001; Hadjikhani, Liu, Dale, Cavanagh, & Tootell, 1998), with a significant degree of colour selective response in V4 (Zeki & Marini, 1998).

Given the relevance of colour information in GCS, it is perhaps surprising that this demonstration of differences in hue detection has not been investigated further with imaging methods, in order to identify what differences in this network confer increased perceptual colour acuity in GCS. Imaging research in GCS has in the most part focused in the verifying the perceptual nature of the synaesthetic colour experience by focusing on the activity of V4 evoked by synaesthetic colour. V4 activation in response to synaesthetic colour has been demonstrated in some synaesthetes (Hubbard & Ramachandran, 2005; Nunn et al., 2002), however, this key result has not been systematically replicated (e.g. Gray et al. (2006); Rich et al. (2006); Rouw and Scholte (2007)). It has been suggested that failed replications may be the result of methodological or analytical differences (Rouw, 2011), however it is possible that phenomenological variability in the synaesthetic experience may also contribute to the degree of colour area activity.

1.1.2.1 Phenomenological evaluation of the GCS experience

Previous attempts to understand the phenomenological experience of GCS have been limited to grouping synaesthetes into projector versus association categories through the completion of questionnaire measures (e.g. Rouw and Scholte (2007); Skelton et al. (2009); van Leeuwen, Petersson, and Hagoort (2010); Weiss and Fink (2009)). Although the application of these questionnaires has provided compelling evidence to support the projector-associator distinction (e.g. van Leeuwen et al. (2011)), they have not been developed and validated following the standard statistical analysis methods proscribed for data collection of this type (Rothen, Tsakanikos, et al., 2013). As such, there is room to reassess previously reported inter-subject variability in GCS using data collected by statistically rigorous and validated tools.

Individual differences in GCS phenomenology Grapheme-colour synaesthetes are commonly categorised as either having a projector-like experience, *or* an associator-like experience. Of the two, the associator-type has been found to be most common, with only a minority of synaesthetes self-reporting a projector-like phenomenology (11 % in Dixon et al. (2004)). The existence of a true categorical projector-associator distinction is contested by some (see for example Edquist, Rich, Brinkman, and Mattingley (2006); Ward, Li, Salih, and Sagiv (2007)). However, even if the precise definitions of projector and associator do not reflect a true bimodal distribution in the GCS population, the development of these categories has been beneficial in drawing attention to the phenomenological variability in the GCS population. Heterogeneity in the phenomenological experience of a population

may be expected to show a degree of impact on behavioural or neural data, and thus an improved understanding of individual differences in phenomenology may aid and guide behavioural and neural investigations (Esterman, Verstynen, Ivry, & Robertson, 2006).

Due care and attention is required in the development and interpretation of first-person phenomenological data collected by questionnaires, as the participant is required to perform a certain amount of interpretation of the question wording when providing their answer. For example, when the participant is asked to identify whether their concurrent is experienced 'out in the world', they may answer to reflect the fact that they are aware that the experience is not a 'real-world' event, to demonstrate that they are not delusional or hallucinating (Eagleman et al., 2007). Other potential dangers arise in the use of assumptive terminology, such as the word "projected" itself, as this infers action on the part of the synaesthete. It appears in some cases that a certain amount of ambiguity is included by design in question wording, such as in the use of phrases such as, "as if it were", "floats in space" (Rouw & Scholte, 2007, 2010) or "in your mind's eye" (Skelton et al., 2009). Such vague or indistinct language may reflect a lack of appropriate understanding of the synaesthetic experience, or alternatively a lack of ability to obtain detailed descriptions of the experience. It is also possible that the variability of experience between individuals is so great that it cannot be suitably translated into a simple questionnaire format. On the basis of existing questionnaires, the GCS trait does appear to cluster into two distinct groups (see for example Rouw and Scholte (2010) figure 1), however, there are instances where classification is ambiguous. For example, Skelton et al. (2009) observed that nearly 17% of their study population reported to experience an equal amount of projector-like and associator-like experiences. Given the relatively small population size in their study (12 synaesthetes), it is unlikely that these "undetermined" individuals are unique in their experience. Skelton proposes that these individuals may represent a new subcategory, however it is equally likely that these individuals represent a proportion of the population to which the current projector-associator distinctions cannot be accurately determined through short tick-box-style questionnaires.

The limitations in successful application of the categorical distinctions of projector and associator may suggest that it is more appropriate to consider these phenomenological descriptions as representing a continuous dimension, rather than a categorical one (Cohen Kadosh & Terhune, 2012). In applying a continuous dimension, we may be able to assess evidence for behavioural or neural differences in terms of the properties which correlated with or are predicted by the position of each individual on the spectrum.

1.1.2.2 Neural theories of concurrent induction

The precise neural mechanisms which give rise to synaesthetic phenomena are poorly understood (Spector & Maurer, 2009). A key debate concerns whether the synaesthetic brain features abnormal structural connectivity between inducer-specific and concurrent-specific processing areas (the cross-wiring hypothesis) (Ramachandran & Hubbard, 2001) or whether concurrents are experienced due to a reduction in top-down inhibition between some as yet undefined "multi-sensory nexus" and the concurrent processing areas (the disinhibited feedback hypothesis) (Grossenbacher et al., 2001). Experimental evidence has been provided in support of each of these theories, as described below.

Cross-wiring Theories of cross-wiring propose that the induction of the synaesthetic concurrent is the result of increased connectivity between inducer and concurrent processing areas (Ramachandran & Hubbard, 2001) (see Figure 1.1). This theory may be particularly appealing in GCS, as the inducer (visual word form area - VWFA) and concurrent (V4) processing areas are closely located in the fusiform gyrus (FG). In support of this theory, a number of studies have identified increased grey and/or white matter near the FG, suggesting increased local or long-distance connections. Three investigations have found evidence for increased structural connectivity in the temporal lobe, specifically in the area of the FG, encompassing the VWFA and V4 regions (Jäncke, Beeli, Eulig, & Hänggi, 2009; Rouw & Scholte, 2007; Weiss & Fink, 2009). These investigations used voxel based morphometric (VBM) methods to identify grey matter (GM) differences between synaesthetes and controls in terms of cortical thickness, volume or surface area. VBM methods are interpreted under the assumption that increased cortical thickness, volume or surface area is caused by an increase in the density of neurons. Increased GM in the FG therefore suggests an increased density of neurons in that area, and thus increased local connectivity, in synaesthetes compared to controls. Increased local connectivity may result in direct cross-wiring of the VWFA to V4. Direct structural connectivity has also been implicated in studies employing diffusion tensor imaging (DTI) in order to identify fractional anisotropy (FA) values of white matter. Increased FA demonstrates that diffusion is anatomically restricted in a given direction, which may reflect fibre density, axonal diameter and myelination of white matter. A finding of increased FA in a certain cohort and area is therefore suggestive of increased long range (white matter) connectivity in those participants. Increased FA has been identified in synaesthetes relative to controls in the right inferior temporal cortex, next to the FG (Rouw & Scholte, 2007) and roughly

in the area of V4 (Jäncke et al., 2009). Both Rouw and Scholte (2007) and Jäncke et al. (2009) found the increased FA to be part of a network of local cortico-cortical association fibres in the inferior temporal lobe, running between early visual areas such as V2 and the temporal lobe, in the area of the inferior longitudinal fasciculus which connects the occipital and temporal lobes. Cross-wiring theories are also supported by investigations relating to the speed of V4 activity induction in GCS, as identified using EEG and MEG. Brang, Hubbard, Coulson, Huang, and Ramachandran (2010) reported that above baseline activation within V4 of synaesthetes was almost simultaneous with activation within grapheme processing areas, differing by only 5 ms. Brang and colleagues argue that the almost simultaneous activation of the VWFA and v4 suggests that the two are linked by a direct path, as a more significant lag in transmission would be expected if the connections between VWFA and V4 were indirect (e.g. following the disinhibited feedback hypothesis). The findings of increased GM and FA and the rapid activation of v4 are strongly suggestive of altered structural connectivity in the area of the FG. These findings support the cross-wiring theories of synaesthesia and may account for the BOLD signal response of V4 when synaesthetes are presented with achromatic inducers, suggesting that the direct stimulation of the inducer specific VWFA is accompanied by a structurally mediated spread of activation to the adjacent V4 region. It should be noted, however, that a large number of the group differences in neural structure between synaesthetes and controls identified by Jäncke et al. (2009) only reached statistical significance under low and uncorrected thresholds. It is possible therefore that not all synaesthetes in this sample expressed the differences to an equal degree and thus the purported cross-wired state may not be present in all cases.

Disinhibited feedback Grossenbacher et al. (2001) hypothesised that multisensory regions within the superior temporal or parietal lobes might feature abnormal functional or effective connectivity in GCS, such that the downstream concurrent processing areas are activated via feedback modulation from higher processing areas (see Figure 1.2). Feedback modulation of lower cortical areas is a known feature of normal neural architecture (Shulman, 1997). This theory of concurrent induction has thus been termed *disinhibited*-feedback as it posits the normal feedback modulation to be increased in GCS. By this model, it is possible that any point in the hierarchical processing of visual information may be responsible for concurrent induction, without the need for direct structural differences. Evidence in support of this hypothesis is found in increased the BOLD signal of the temporal and parietal lobes during inducer presentation, suggesting that these upstream

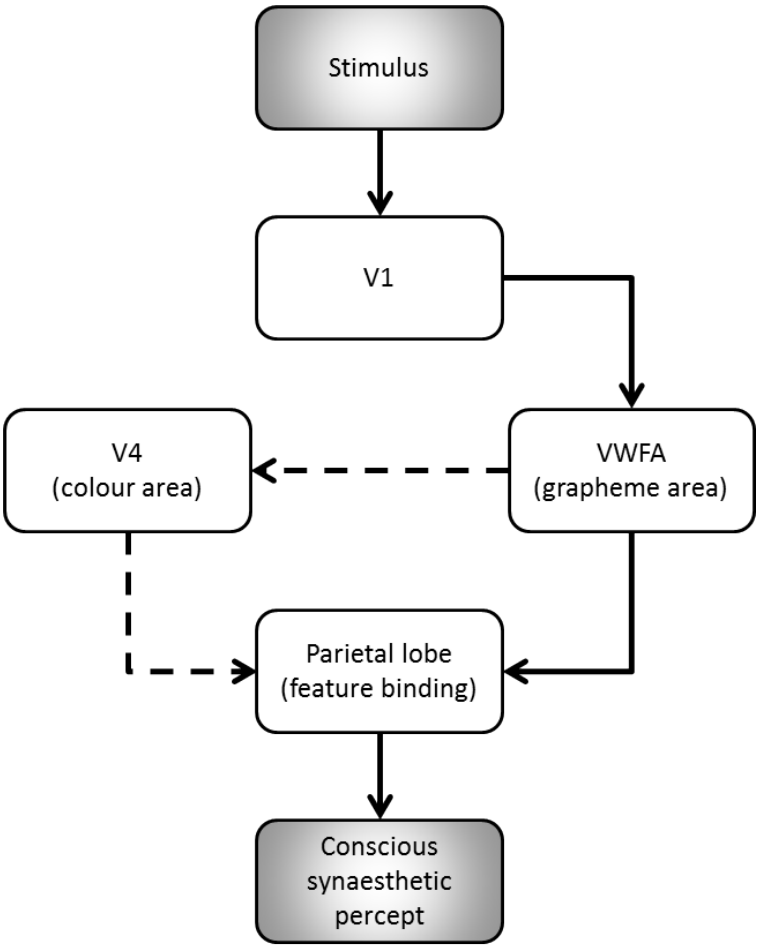


Figure 1.1: Schematic illustration of the cross-wiring hypothesis of synaesthesia (Ramachandran & Hubbard, 2001). Normal functional connectivity (solid lines) illustrates hierarchical processing of visual information from early visual areas (V1) in the formation of a conscious percept. According to the cross-wiring hypothesis, synaesthetes feature abnormal structural or functional connectivity directly between inducer and concurrent specific processing areas (dashed line). The concurrent specific activation is then processed in higher cortical areas, with the two separate features bound in the parietal lobe to form the conscious percept of a conjoined grapheme and colour experience.

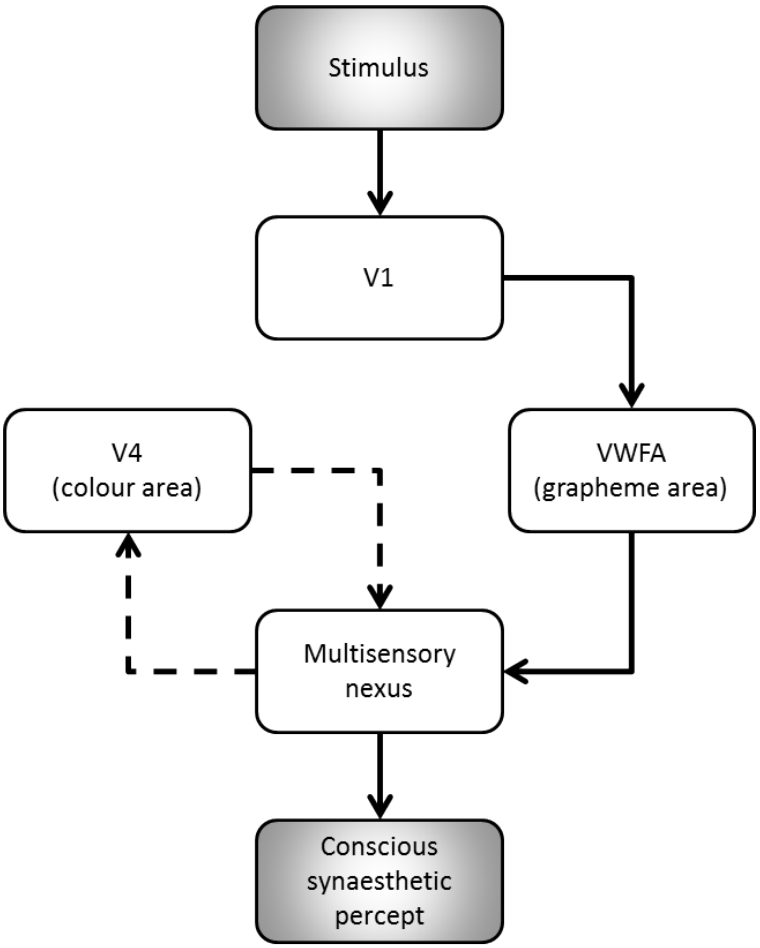


Figure 1.2: Schematic illustration of the disinhibited feed-back hypothesis of synaesthesia (Grossenbacher et al., 2001). Normal functional connectivity (solid lines) illustrates hierarchical processing of visual information in the formation of a conscious percept. According to the disinhibited feedback hypothesis, synaesthetes feature abnormal effective connectivity between higher and lower level processing areas, thus activation which reaches a 'multisensory nexus' is selectively reverted to the concurrent processing area (dashed line). The concurrent specific activation is then processed normally and the two separate features are bound to form the conscious percept of a conjoined grapheme and colour experience.

processing areas is a contributing factor in the generation of the concurrent experience. Sperling, Prvulovic, Linden, Singer, and Stirn (2006) found the superior and inferior temporal gyrus to be activated in synaesthesia and Weiss, Zilles, and Fink (2005) found the both the anterior interparietal sulcus (AIP) and caudal interparietal sulcus (CIP) to be activated. The AIP and CIP are known to be involved in polymodal processing (Grefkes, Weiss, Zilles, & Fink, 2002) and the superior temporal lobe has a suggested role in object colours naming (Zeki & Marini, 1998). Thus it is possible that in the GCS experience, the activation of these areas in the processing of the letter form is propagated back to V4.

Previous experiments have attempted to determine whether GCS is the result of cross-wiring or disinhibited feedback by indirect behavioural effects. For example, evidence that concurrents enable the 'pop-out' of inducers amongst a background of non-inducers would favour cross-wiring connectivity over top-down disinhibition, as pop-out is considered to result from low-level perceptual interactions and does not normally engage higher cortical areas. However, there is no clear evidence for the pop-out of concurrents in GCS (Mattingley, 2009), rather, current evidence indicates that some degree of spatial attention and thus higher level processing is required in the formation of a concurrent experience (Ward & Mattingley, 2006). Evidence in favour of the disinhibited feedback hypothesis is supported by the experimental induction of synaesthesia during hypnosis (Cohen Kadosh, Henik, Catena, Walsh, & Fuentes, 2009) or hallucinogens (Hollister (1968) in Cytowic and Wood (1982)). It is proposed that if synaesthesia is mediated by the formation of new cortical connections (as suggested by the cross-wiring hypothesis) then acquired or transient synaesthesia would not be possible over such a short period of time. However, it is possible that hypnotically induced synaesthesia is the result of different mechanisms compared to those responsible for innate synaesthesia. Also, while new structural connections are indeed unlikely to be established during hypnotic suggestion, this does not rule out the transient formation of novel functional connections. Structural and functional connectivity interact, but need not be identical, with dynamic transient functional connections supported by a stable underlying structure (Seth, 2008).

A further outstanding question in the neural literature of GCS relates to how synaesthetes are able to dissociate concurrents from their perceived external world. Synaesthetes are not regarded as delusional, that is they understand that their concurrents do not exist in the external environment. It is assumed that on a daily basis they are required to resolve the conflict between the external presentation of a letter with its associated veridical colour, from their own internal colour representation. Synaesthetes have been

demonstrated to experience Stroop-like interference between the veridical colour of the external stimuli and the synaesthetically induced colour, with concomitant increases in reaction times in veridical colour naming if inducers are presented in colours which are different from (incongruent to) their synaesthetic colour for that item (e.g. Dixon et al. (2004); Mattingley, Rich, Yelland, and Bradshaw (2001)). In imaging experiments, such behavioural tasks have demonstrated the engagement of cognitive control areas including the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) (e.g. Weiss et al. (2005)). Although it might be necessary to invoke such cognitive control mechanisms when performing a Stroop task, such a task is not common-place outside of experimental settings. The degree to which cognitive control is engaged in the duel processing of veridical and synaesthetic colours might therefore be inflated in Stroop tasks. As such, Stroop-related effects in synaesthesia may reflect a consequence of additional cognitive load in dual colour processing, but it is not necessarily relevant to understanding the processes involved in the generation of the synaesthetic percept *per se*.

1.2 Thesis outline: Investigating individual differences in synaesthesia

In this thesis, we have addressed the issue of phenomenological variability in the expression of synaesthesia using both qualitative and fMRI methods. In Chapter 2 we report detailed phenomenological analysis of the SFS experience of a single subject, in order to determine the level of detail in phenomenological descriptions which may be obtained by second-person methods, and assess the impact of this information on future behavioural and neural investigations of SFS. In Chapters 3 to 5, we address outstanding issues in the neural profile of GCS using functional activation, context specific functional connectivity and resting state functional connectivity analysis. We address conflicting reports of colour area activation during synaesthetic colour processing, along with the functional networks which support the synaesthetic experience at both the trait level (networks which are assumed to be common to all grapheme-colour synaesthetes, and how they differ from controls), and how those networks are modulated by individual differences in phenomenology. We assess evidence for the bottom-up and top-down theories of concurrent induction, along with how these theories may be differentially implicated, through assessment of individual differences. Throughout this thesis, we emphasise the interpretation of experimental effects in light of the best available data regarding the phenomenological experience of the

participant, exemplifying the neurophenomenological approach, and combine fMRI with phenomenology in order understand the conscious experience of synaesthesia.

Chapter 2

Extended case study on the phenomenology of spatial form synaesthesia

2.1 Chapter summary

A thorough understanding of the experiential phenomenology of a trait is required in order to effectively design and interpret experimental investigations. The phenomenology of spatial-form synaesthesia (SFS) is ordinarily expressed in terms of spatial relationships between the inducer (number, letter, months etc.) and the concurrent (a spatial localisation and representation of the inducer). However, we hypothesised that using appropriate second-person techniques, the phenomenological experience of SFS could be obtained to a far greater detail than previously identified, and that such detail could be informative in future investigations of the trait.

Here we report an extended phenomenological investigation of SFS in a single case (AB). We used the Elicitation Interview (EI) method to facilitate repeated exploration of AB's synaesthetic experience. During an EI the subject's attention is selectively guided by the interviewer in order to reveal precise details about the experience. Qualitative analysis of the interview data was conducted in order to identify the temporal and synchronous aspects of the experience. This was the first application of an EI to synaesthesia, and the first systematic investigation of the second-person experience of synaesthesia more generally.

Detailed analysis of the resulting 9 hours of interview transcripts provided a comprehensive description of AB's synaesthetic experience, including several novel observations. For example, we describe a specific spatial reference frame in which AB's concurrents occur, which involves 'mental' and 'physical' rooms, and between which he is able to switch voluntarily. Exemplifying the EI method, some of our observations were previously unknown even to AB. For example, AB initially reported to experience concurrents following visual presentation, yet we determined that in the majority of cases the concurrent followed an internal verbalisation of the inducer, indicating a novel auditory component to spatial-form synaesthesia. This finding is congruent with typical rehearsal of inducer sequences during development, implicating cross-modal interactions between auditory and visual systems in the genesis of this synaesthetic form. These descriptions move beyond rudimentary graphical or spatial representations of the synaesthetic spatial form, thereby providing new targets for neurobehavioural analysis.

2.2 Introduction

2.2.1 Spatial-form synaesthesia and qualitative research

Spatial-form synaesthesia (SFS) is a trait in which affected individuals experience ordinal sequences such as numbers, letters and calendar months as occupying precise locations in extended areas of space (Price, 2009; Ward, 2013). In SFS, visual presentation of a letter, number, month etc. leads to (induces) a concurrent percept of that item in an external spatial location and cues spatial attention to that area (Price & Mentzoni, 2008; Smilek, Callejas, Dixon, & Merikle, 2007; Teuscher, Brang, Ramachandran, & Coulson, 2010). Each form is defined by the inducer type, for example where inducers are numbers, the concurrent is known as a 'number form', equally calendar items induce a 'calendar form'. Despite affecting up to 20% of the population (Mann et al., 2009; Sagiv et al., 2006), our understanding of the visual phenomenology of this experience is generally limited to the reproduction of schematic spatial representations of concurrents (see for example Figure 2.1). The primary focus of SFS researchers has been the behavioural verification of the spatial relationships that subjects report to exist between concurrents. For example SFS has been demonstrated to produce a deviation from the normal Spatial Numerical Association of Response Codes (SNARC) effect, in which normal subjects are faster to respond to low numbers if they are presented on the left (e.g. Hubbard, Ranzini, Piazza, and Dehaene (2009)). SFS has also been shown to reduce reaction times to items presented in positions congruent to a concurrent spatial location (e.g. M. Jarick, Dixon, Maxwell, Nicholls, and Smilek (2009)). These findings provide objective correlates of the subjective descriptions of SFS and show the perceptual experience to have measurable behavioural effects.

Some of the most complete published introspective reports of SFS come from investigations conducted by Seron et al. (1992), however the qualitative study of SFS was initiated by Galton (1880). Seron et al. (1992) collected spontaneous written introspective reports from 26 SF synaesthetes and uncovered a number of features which have been afforded little attention in subsequent research. For example, one of the subjects in the Seron et al. (1992) investigation (JB) indicated that defined sections of his number form had a black background and white digits whilst other sections had a white background and black digits (see Figure 2.4). Nineteen of the Seron et al. (1992) subjects also report that once "activated', a concurrent could not be moved. Subjects also reported being better able to "make use' of their representation where they had a free "visual field", e.g. when their eyes were closed, and that the "vividness" of the number concurrent increases when

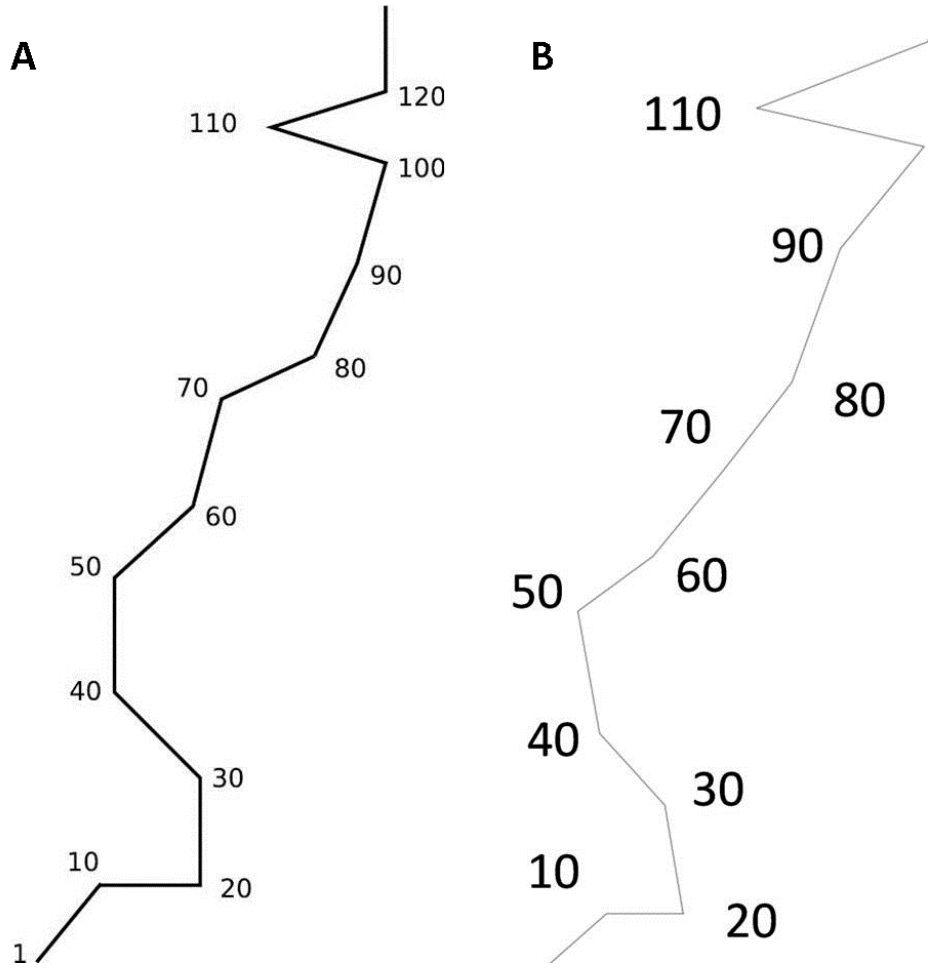


Figure 2.1: AB's number form as produced (A) at the start of this investigation and (B) 22 months later.

the subjects concentrate on it (Seron et al., 1992, p174). One these subjects also reported to automatically experience the concurrents immediately surrounding the induced item, although these adjacent numbers were "a bit less salient" (Seron et al., 1992, p180). It should be noted that introspective reports of Seron et al. (1992) were collected via a questionnaire with both open-ended and "yes/no/maybe" questions, therefore the detail of the phenomenological features presented in his report are limited. Seron et al. (1992) do however appear to have re-ignited the interest in the exploration of this trait and conclude that the "genuineness of the number representations" remains the primary open question (Seron et al., 1992, p185). 20 years later, the majority of published research on SFS is focused towards establishing the reliability and behavioural impact of SFS, with little regard to the phenomenal aspects which may shed light on other processes which have been shown to be modulated by SFS, e.g. visuospatial working memory, visuospatial imagery, sequence representation and memory for personal or historical dates (see Price and Mattingley (2012) for a review).

Here, we obtain an extended phenomenological description of SFS in a single case, demonstrating that qualitative second person techniques can be used to gather first-person information about a perceptual or cognitive experience of SFS and that such information may be used to guide the quantitative investigation of the trait. We reason that a detailed knowledge of SFS phenomenology will inform behavioural and neurological investigations in this topic and aid our understanding of the relevant cognitive processes in the non-synaesthetic population. Such detailed phenomenology-based investigations may be beneficial in constraining accounts of development of SFS. In this paper we demonstrate that phenomenological descriptions may be reliably obtained from subjects through the application of the Elicitation Interview (EI) (Vermersch, 1994), which may be appropriately analysed using Grounded Theory (GT) approaches. By demonstrating the ability of these methods to produce meaningful and rich contributions and new insights into SFS, we highlight the importance of the subjective experience when informing and analysing behavioural and neurobiological experiments. To promote familiarity with the EI method, the reminder of this introduction will describe the EI and relevant assumptions of data collection and analysis.

2.2.2 Elicitation interview

The EI technique is derived from the phenomenological tradition of Husserl, namely the study of phenomena which appear during acts of consciousness. In performing an EI,

the trained interviewer directs the attention of the subject to precise aspects of their phenomenological experience (Vermersch, 1994) to guide introspection. In this manner the subject can access perceptual or cognitive events which had previously occurred beneath reportable subjective awareness. EI has previously been applied to increase awareness of epileptic prodrome features as an early warning of a seizure onset (Petitmengin, Navarro, & Quyen, 2007) and to understand the adaptation strategies of elderly drivers (Cahour, Forzy, & Martin, 2010) (see also Maurel (2009) for other applications and Froese, Gould, and Barrett (2010) for a review of the latest research using second-person methods). A full and detailed method for the conduct of an EI has been presented elsewhere (e.g.)Petitmengin (2006). A brief overview of the assumptions and priorities in data collection are provided next to highlight the unique properties of this method.

The assumptions of EI make it particularly suited to dissecting processes which occur automatically or with little conscious effort, but which also retain a cognitive 'anchor' upon which to ground the interview. For example, "How do you recognise your friend in the street?" may be a suitable area of investigation, as the instantaneous moment of recognition acts as a single cognitive event is the culmination of a multitude of automatic processes. Conversely, "How do you know when to blink?" may not reveal such depth of accessible unconscious activity as the blink is primarily the result of physiological stimulation. Where the application of EI uncovers previously pre-reflective aspects of experience, we may then investigate these features with a battery of existing behavioural or neuropsychological paradigms. EI is also particularly suited to the investigation of recent events, rather than those requiring significant retrospective access. A potential risk in the collection of first-person data is in the unintentional retrospective transformation of events, as demonstrated by experimental false memory induction (e.g. Loftus and Pickrell (1995)) and false recollection (Greenberg, 2004). The specific language used by participants in reporting false memories will however allow a skilled interviewer to recognize infidelity in the report and exclude the relevant section from analysis (Froese, Gould, & Barrett, 2011). Steady-state experiences such as synaesthesia may engender high fidelity reports as the event can be reported immediately as it unfolds, rather than retrospectively.

During the EI, we aim for the subject to reach and maintain an 'evocation state' through interviewer-led direction of attention to the different sensory registers. Evocation is a deep introspective state in which the subject is in 'direct contact' with their experience and re-living it as they speak. Although the original moment may have passed in but a few seconds, we are able to prolong and extend the experience during the evocation state

through subtle use of language and cues, thereby increasing the reporting access to instantaneous events. At all times, the interviewer is mindful of monitoring and maintaining the evocation state of the subject to ensure they are reliably verbalising the experience and not their beliefs about the experience. This is achieved by active and open questioning and rephrasing of the subjects own statements, to draw attention to specific aspects which are generally overlooked in normal discourse. A positive evocation state is suggested by slow and considered speech, avoidance of generalisations, a distant or unfocused gaze and often language in the present tense (the subject may say, "I can see" rather than "I remember seeing"). Examples of good practice in bracketing and maintaining evocation are provided in the Methods section.

In the present study, the interviewer and subject freely explored the subject's synaesthetic experience in order to gain a comprehensive understanding of what the subject experienced both reflectively and pre-reflectively during a synaesthetic event. The results of the EI were analysed following the prescribed method, involving successive iterations of aggregation and abstraction of themes, schemas or structures of the experience. This process is similar in kind to the more widely practised GT analysis of qualitative data (Glaser & Strauss, 1967).

2.2.3 Grounded Theory analysis

The aim of the EI analysis is to develop 'rules' and descriptions of the experiential structures presented in the data, in a manner similar to GT analysis as commonly applied to qualitative data in social sciences research. GT analysis is used to generate a hypothesis to explain behaviour patterns and discourse content. The hypotheses are 'reverse engineered' in that the data are collected first and then later explained by the hypothesis (Glaser & Strauss, 1967). The process involves the identification of themes or topics of interest in the interview transcripts and the formation of a hypothesis for future refinement and verification in successive rounds of data collection. Data collection and analysis are often conducted simultaneously, such that theories generated in the first batch of data may be immediately refined in the next round. During analysis, themes and sub-themes identified are grouped into concepts and categories to form theories. Sampling and data collection are required to continue until each category is saturated, that is until no new information is being incorporated into the theory (Cutcliffe, 2000).

2.3 Material and Methods

2.3.1 Participant

The subject (AB) is a 30 year old, right handed male with no medical history of psychological or neurological trauma. AB reported to have experienced spatial form synaesthesia for numbers, days of the week and months for as long as he could remember. Prior to interview, no facet of AB's SFS was identified as particularly remarkable or out of the ordinary. To test the consistency of his SFS, AB was asked to reproduce his number and month forms at the start of data collection and again 22 months post interview. These two schematics were considered to be sufficiently similar to confirm AB's synaesthesia for these forms (see Figure 2.1).

Throughout the following sections, we have made extensive use of direct quotations from interview transcripts in order to convey the essence of the interview conduct and mode of questioning. Quotations are referenced with the interview date in the format YYYYMMDD and the paragraph number in the transcript. For example the reference "(20100408_123)" refers to paragraph 123 on the transcript of the interview conducted on 08/04/2010.

This investigation was conducted to demonstrate that qualitative EI data can provide meaningful routes of investigation for future behavioural or neurological investigations of SFS. An investigation with a single subject is sufficient to generate testable hypotheses in this regard, while longitudinal data collection enables the assessment of the fidelity of the reports based on consistency between sessions. The conclusions drawn are appropriate to our subject and further work will be required to demonstrate their applicability to a wider population.

2.3.2 Conduct of the interviews

Interviews were conducted by a trained and experienced EI practitioner. 9 hours of interview were conducted over nine non-consecutive sessions spanning two months. The interviews were conducted in a private room and recorded following the informed consent of the subject. The nature and purpose of the EI method was defined at the beginning of the first interview session, with the interviewer highlighting the requirement for the subject to describe the experience in detail, with an emphasis on the temporal unfolding of the experience. The subject was also reminded of the interviewers role in guiding and maintaining the focus of the subject's attention, suggesting that these particular skills may

develop as the series of interviews progress (20100215_2). Each interview session began by revisiting the features of interest in the previous or addressing any topics which had been raised informally between interviews.

2.3.2.1 Maintaining the subject's focus

The interviewer used active questioning and reformulation of the subjects own words in order to maintain attention on a single instant or aspect of the experience, as exemplified below.

1. AB: *Ahm... I'm looking at it... at the moment I'm projecting it onto the screen in front of me and just... It's all on that screen.* INTERVIEWER: *So if you look at that screen...* (20100215_45-46).

2. AB: *I think it mainly is green, and there's appearing a kind of a wall...*(20100222_20). AB: *So, so you can sort of see a floor underneath the five, and then there's kind of a wall... ahm.*(20100222_22). INTERVIEWER: *And if you focus on the wall and the floor, and try to keep your focus there, how does the periphery look? You said it's undefined, or does it go off into the distance?* (20100222_32).

In (1) the subject refers to concepts of "projecting" and "screen", both of which have not been explored at this stage. In order to gain a description of what the subject means by the use of these words, the interviewer simply asks AB to look at the screen and describe what he sees. In (2) the interviewer uses the terms "wall" and "floor" as the subject did. This reuse of the subjects own words serves to maintain and focus his attention on these specific features.

2.3.2.2 Bracketing for bias reduction

Bracketing is designed to minimise the impact of interpretive bias by the subject and interviewer. The interviewer used only open questioning without leading. The subject's reporting bias was reduced by maintaining the appropriate evocation state under which beliefs and analogies etc. should be minimised. Data was removed from analysis if the interviewer's questioning was deemed inappropriate or leading. Examples of bracketed or excluded data are given below for clarity.

1. INTERVIEWER: *Can you say something of where this is being presented to you?* AB: *Yeah, I think I'm projecting a mental image in front of me. INTERVIEWER: Okay, well maybe we'll come back to that later* (20100215_16-23).

2. INTERVIEWER: *But interestingly enough, the number line, when I asked you to have one behind you, latched onto the floor* (20100329_206).

In (1) the interviewer identified a 'belief' or theory that the subject held about his experience. The subject says, "I think I'm", demonstrating that he believes he is performing an act which he has termed "projecting", rather than providing a description of the content of the experience. The interviewer chose to immediately divert from this description and return to the topic at a later time. In (2) the interviewer allowed their own beliefs about the experience to enter the discourse. The term 'latching' suggests a selective action towards an object and is not used by the subject himself. The line of questioning suggests that the interviewer formed this belief earlier during the course of the sessions, however this is the only time in which the belief is imposed upon the subject. This section of interview and all related discourse were removed from analysis.

2.3.3 Analysis

Interview data was first transcribed and then followed successive rounds of coding, aggregation and abstraction, as illustrated in Figure 2.2. Analysis of data was conducted blind by a researcher with no prior theoretical knowledge of SFS. As suggested in Froese, Gould, and Seth (2011), a blind analysis method was chosen to enable the independent observation of any interviewer bias and ensure that the theories devised are only those which are latent in the data. Analysis was conducted by a trained EI practitioner.

Interview dialogue was transcribed verbatim, including stammers and interjections, by a contracted professional transcription agency. Transcribers additionally noted changes in pace, intonation or volume of speech, where specific emphasis is placed on words and significant or lengthy pauses, to assist the analyst in monitoring the evocation state of the subject. Transcribers were blind to the nature and purpose of the interviews.

All transcripts were read once by the analyst to identify initial themes or topics to describe the content of the discourse. Themes were then summarised by short statements and a code devised to represent the theme. The code was then attached to relevant sections of the transcript using QSR NVivo 9 software (QSR International, 2010). Once all data relevant to a particular theme had been coded, the theme summary was revised and new sub-theme codes were devised. A second round of coding was then conducted using sub-themes.

The coded transcript was exported with paragraph references into Freemind mind mapping software (FreeMind Project, 2010), clustered by themes and sub-themes. Individual

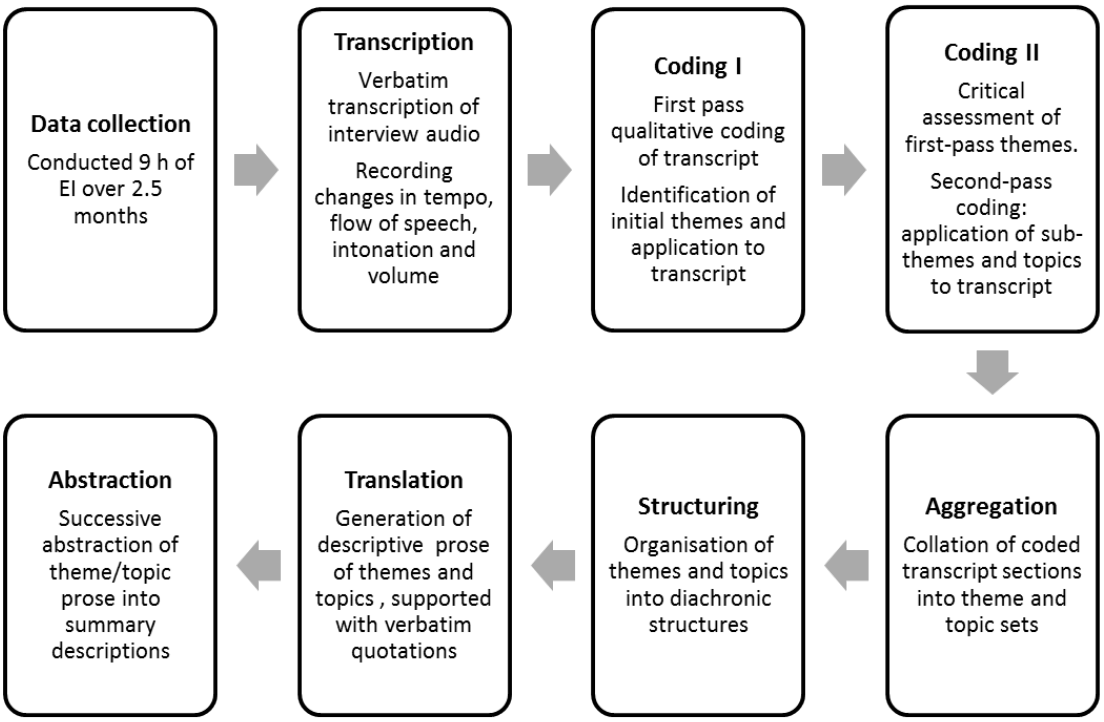


Figure 2.2: Schematic of data collection and analysis process in Elicitation Interview.

excerpts were systematically arranged into appropriate headings (with further subheadings generated where necessary) to ensure all references to a topic were collated. The tree-like presentation of the mind-mapping software enabled a systematic analysis of the temporal development of events (diachronic structure) and aggregation of simultaneously occurring aspects of the experience (synchronic structures).

All data were assessed for validity according to the principles of EI by confirming that the report related to the experience as it happened and did not contain comments or thoughts about the experience on the part of the subject or interviewer. Reports were also examined for consistency over the interview sessions. Any reports found to be incompatible with the EI requirements or inconsistent across sessions were excluded from analysis. Themes were validated post hoc by reference to existing literature on SFS phenomenology, where the literature was assessed for reported descriptions which were in accordance or disagreement with the themes deduced.

Each reference within a cluster was reorganised into diachronic and synchronic structures where possible. Ordered clusters were then summarised into short sections of prose which reported the content and context of the cluster. Abstractions were made for every level of the map from the lowest to the highest level of the theme (for example the de-

scription of the concurrent contexts includes 4 levels of abstraction, over 77 separate sub-headings - see Appendix A.1). This abstraction made it possible to gain a coherent and concise report of the subject's experience whilst bearing in mind all relevant reported features. The aggregations and abstractions of coded transcript are available in Appendix A.1.

2.4 Results

The EI sessions provide comprehensive descriptions of the first-person experience of SFS for subject AB, including aspects of which he was previously unaware. Analysis of EI data identified several themes of potential importance to SFS research, particularly regarding possible developmental trajectories of this trait. We next illustrate here the topics of discussion in the discourse and provide phenomenological descriptions of AB's different synaesthetic forms. The themes and descriptions may not be exhaustive of the SFS phenomenology for this subject, rather they reflect the developing discourse of the interview sessions.

2.4.1 Discourse content

Table 2.1 outlines the coverage of individual codes in the transcripts after the second pass in NVivo. The majority of the discussion was related to AB's number form (55.8% of all discourse) as opposed to his calendar or alphabet forms (15.5% and 10.3% respectively). Some of the most significant phenomena were only covered briefly during interview (for example in the original coding only 1.4% of the transcripts related to interference from the physical room, see Section 2.4.3.1) however when these brief statements are collated and examined in terms of their interactions in the data as a whole, we find them to be underpinning much of the synaesthetic experience itself. This and other themes in AB's SFS experience are presented next.

2.4.2 Form descriptions

The synaesthetic forms examined in the course of these interviews include a spatial number form, experiences of mathematical concepts such as pi, a spatial alphabet form, a spatial form for age and separate spatial calendar forms for years, months of year and time. This data provides the most comprehensive descriptions of the visual synaesthetic experience of a single subject available to date.

2.4.2.1 Number form and mathematical concepts

Number concurrents generally appear as black Arabic symbols in an Arial-like type face. Certain numbers (notably five and fifty six) are described as having "metallic" (20100222_247) or "velvety" textures (20100222_321) and also surface patterns such as "cross hatching" (20100408_67) or pockmarks "as if the ink has come away in lots of places" (20100320a_246).

Table 2.1: Coding summary report. The percentage here represents the proportion of all interview data which were coded to a particular theme or sub-theme. Items are listed in order of greatest total coverage for a theme with sub-themes and topics contained therein also listed in descending order. Note that a reference may be coded to two or more items where a particular section of discourse is relevant to a number of different themes, thus the total coded coverage does not sum to 100%.

Theme	**Coverage as % of all coded discourse**
Forms	**101.2**
Number	55.8
Mathematical constants	*15.0*
Arithmetic	*2.6*
Fractions	*2.1*
Calendars	15.5
Age	*6.1*
Time	*5.1*
Year, month & date	*4.1*
Alphabet	10.3
Stability	**6.1**
Attention	3.2
Knowledge	1.5
Interference from physical room	1.4
Visual imagery	**9.9**
Backgrounds	**7.8**
Multiple representations	**7.7**
Controllable acts	**6.4**
Perspective	**5.1**
Patterning	**4.6**
Inducer-concurrent relationships	**3.6**
Autonomous language	**1.0**
Scalable	**0.6**

The texture or patterning may move around and change although the number itself remains static.

Both fractions and decimals are viewed in the correct position relative to their surrounding numbers. Different notations of fractions can be generated on request (e.g. 1.5 may be represented as 3/2 or 6/4). Different notations of the same fraction appear initially as though superimposed on top of each other. Large numbers (in the thousands) appear with the comma separator.

When discussing mathematical concepts, multiple defining equations and graphs appear automatically following a related inducer. For example, when discussing Planck's constant the subject reports, "I got E equals H bar times F.... And just underneath I've got H bar times a Greek nu as well [...] I've got H bar equals H over 2 pi." (20100320a_219-224). These concurrents include not only visual experiences of letters and numbers to multiple decimal places, but also by their associated graph forms with spatial segregation, for example, "INTERVIEWER: What about E? AB: So I've got a flash of the exponential curve and then I saw the letter E, it took a while for the equal sign and numbers to appear but then they are there." (20100320a_71-72). "INTERVIEWER: If you go back to E, do you see the two graphs that you mentioned? AB: Yeah, kind of one over here and one over there." (20100320a_137-138).

Numbers such as pi are experienced in their correct position in relation to the integer on the number line. A black area or "black hole" (20100229_200) is experienced when the concept involves a number with infinite decimal places, with the decimal numbers trailing towards the black hole, "sucking up all those infinite digits ... just sort of get them out of the way" (20100229_200). The black hole is flat and AB can change his perspective to view it from behind (20100229_122).

2.4.2.2 Alphabet form

AB's synaesthetic form for the alphabet initially appears as capital letters (20100329_215), in an Arial-like type face (20100329_337-339) with a "ghost-like" translucency (20100408_313) and with reproducible a spatial relationship between alphabet items. Specific patterns or textures are generally not reported with the letter form, however following close inspection of the letter B it is described as though "it's made of ribbons attached to each other" (20100408_329).

2.4.2.3 Ages

AB experiences concurrents similar to his number form when exploring concepts of age. AB reports however that the two experiences of age and number concurrents are differentiated because age numbers (e.g. twenty eight) are more often used in the context of age rather than pure mathematics (20100320b_90).

The concurrents elicited by inducer concepts of prenatal ages (conception to birth) are accompanied by static visual scenes of embryonic development representing early conception and a hospital scene with a woman in labour representing birth (20100320b_103-138). These scenes have precise spatial relations to one another and differ from a visual memory by AB's adoption of a dissociated position within the scene. At birth (age 0), the pictorial scenes revert to the normal number form-like experience. Early ages are experienced in months, i.e. 6 months, 12 months, 18 months old, rather than fractions of years.

2.4.2.4 Calendars

AB reports a spatial form for calendar aspects such as years, months and time. His year form is similar to his number form, but there is no comma separator (e.g. the concurrent '1,995' refers to 'one thousand, nine hundred and ninety five', whereas the concurrent '1995' refers to the year 'nineteen ninety five'). The context of the inducer presentation regulates the form perceived, for example the auditory inducer "nineteen fifty six" was presented whilst exploring the number form and automatically triggered the calendar form (20100320a_237). AB is also able to describe and draw his spatial form for the more abstract year inducer of 4000 BC, including an inflection point between BC and AD.

AB's spatial form for months includes the experience of digits and a line arranged circularly with August at the top, progressing clockwise to February at the bottom. Within the months themselves each ten day segment follows a specific direction on the line such that AB can identify a date not only by the position of that month in relation to the others but also by the direction of the numbers on the line surrounding the date.

AB reports a synaesthetic clock with multiple different forms, including: an analogue clock face with hour and minute hands, minute markers and larger hour markers; an orange digital clock with a flashing semicolon for seconds; an alternate digital clock in a separate area of space with a different type face. In directing his attention to different aspects of the analogue clock, AB is able to induce the experience of digits on the clock face where there were none before and report the apparent motion of a second hand as it flashes "in and out of existence" (20100320b_16-18) each time his attention returns to it.

2.4.3 Themes

The themes identified in the EI go beyond basic descriptions of the subject's SFS as they address precise aspects of the experience and how the experience unfolds. Seven main themes were identified from the interviews, as illustrated in Figure 2.3. For brevity, only a proportion of these themes will be presented here. The reader is directed to Appendix A.1 for a web link to download to an interactive expandable map with descriptive abstracted prose of all themes and their supporting verbatim interview quotations.

2.4.3.1 Mental room

AB describes his synaesthetic percepts as existing in a "mental room" (20100320a_108) as opposed to the physical room which simply refers to the room in which the interview was conducted and contains normal (non-synaesthetic) visual experiences (20100408_193). The percepts in the mental room are "superimposed" on the physical room (20100408_137); they have the same physical location as items in the mental room, but the mental and physical exist as if in two "different dimensions" (20100408_163; 20100408_165; 20100408_189), for example, the concurrent percept may be experienced as if they were positioned on the table top of the physical room.

AB reports that he can switch his attention between the physical and mental rooms by forced effort (20100320a_108) or defocusing his eyes and "looking into space" (20100408_33). AB retains an awareness of the physical room whilst looking at the synaesthetic percepts (20100320a_112) although the physical room appears "out of focus" (20100320a_114) similar to a normal experience of an item in peripheral vision (.ibid).

The physical room appears to hold more salience than the mental room such that objects in the physical room obscure synaesthetic percepts or make them weak and vague: "*...if there's an object in this [physical] room, in the same place as one of the numbers are in the other [mental] room, then I see the object rather than the number*" (20100408_195). This effect of physical interference extends into the visual presentation of an inducer, where AB reports having to look away from the "distracting piece of paper" (20100408_13) in order to experience his alphabet form: "it's almost like the actual physical H can't be part of the mental alphabet" (2100408_23). Similarly when AB is shown a number inducer he reports difficulty in perceiving a stable concurrent when viewing the number written on a page and states that the experience of visual induction is "very different from when you are telling me to think of the number " (20100408_65-67). Concurrents also tend to be located in areas of space where there is little interference from physical objects, such as aligned

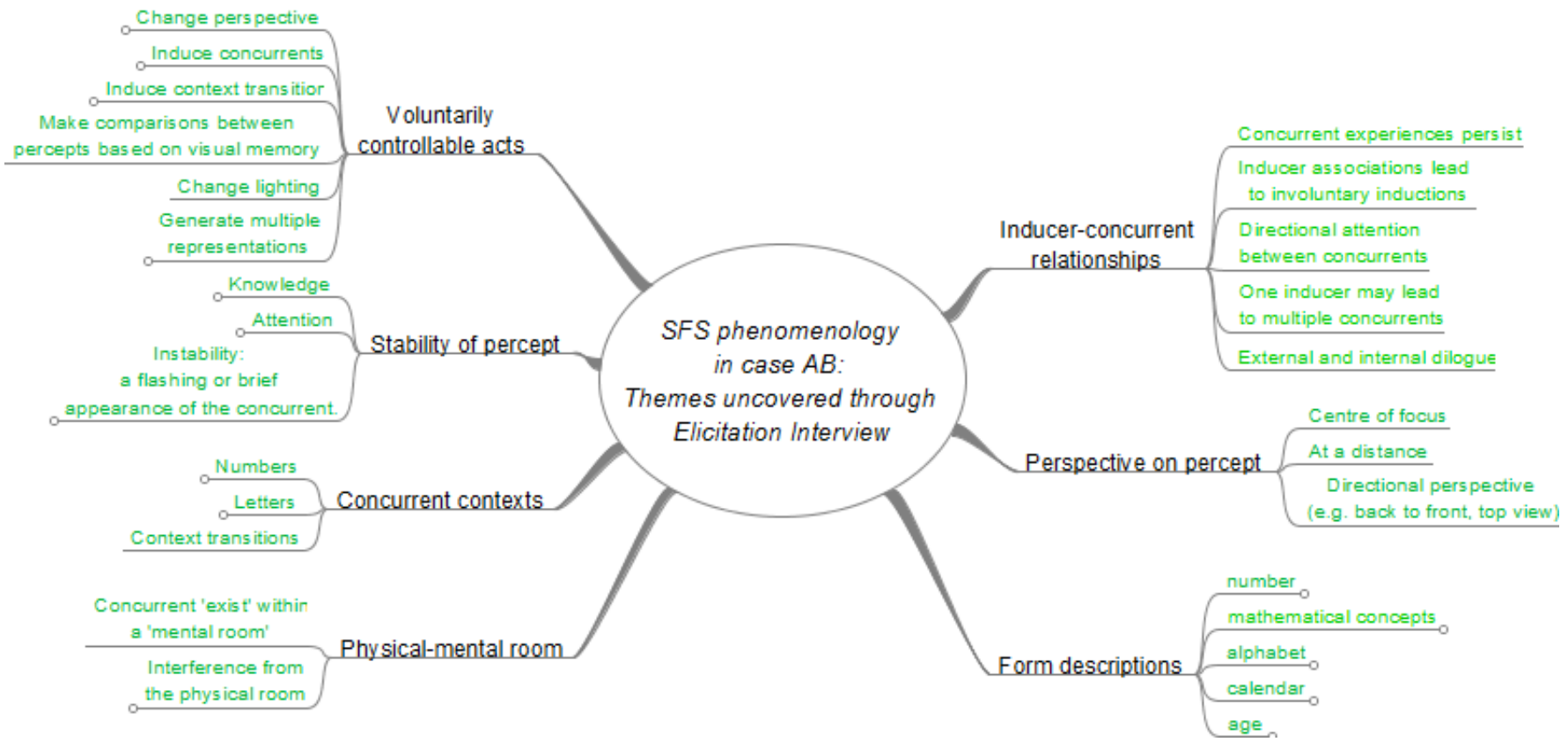


Figure 2.3: Map of themes and sub-themes derived from the EI interview data with case AB.

with the top of an empty table (20100329_89) or in an area of clear space (20100329_107; 20100415_238).

2.4.3.2 Inducer-concurrent relationships

The EI has revealed subtle aspects of the concurrent induction process which have not been reported elsewhere. For example we find that AB makes substantial use of inner speech during induction of a concurrent presented visually and also in directing spatial attention between concurrents. We also find that concurrents may be induced by association with a directly induced item, multiple representations of the same concurrent may be experienced following a singularly induced item and the experience of a concurrent may persist even when attention has been directed elsewhere.

External and internal dialogue Auditory presentation appears to be the most effective induction method for AB's synaesthetic percepts. The audibly induced item is accompanied by those surrounding it in sequence (the induced experience of a two will be accompanied by a one and three in the correct positions) and repeated mention of an inducer appears to increase its stability (20100408_41) (see Section 2.4.3.3). 'Thinking about' an inducer will also lead to the experience of a concurrent (20100305_142) and we find that this thought process often involves inner speech (20100408_48-51). On other occasions AB reports to visualise a concurrent to induce a true synaesthetic experience (20100222_261-263).

Directional attention between concurrents AB reports that if he allows his eyes to move freely along the line of the number or alphabet form, he can see as many or as few concurrents as he chooses (20100329_251). Directing attention may also involve inner speech, for example AB reports in one instance that during this act of 'looking for a concurrent' he says to himself: "right I'm going to look for the 4 now!" (20100408_138). It is possible that this internal monologue is experienced as an instantaneous thought which becomes realised as inner speech through the EI process.

AB also has a strong prior knowledge of where each concurrent should be located in relation to another in the same form. Redirection of attention based on prior knowledge also involves inner speech, for example AB reports "Normally it's like I say to myself, "OK, it's a three, so down to the left of three there should be a one and two. And then, well there they are." (20100408_93) .

Associations lead to involuntary inductions Concurrents may also be experienced if they are related to the induced concurrent through normal associative mechanisms, for example when "a physical constant [...] Like the speed of light" (20100320a_195-196) is presented as an inducer, it also caused the rapid and automatic experience of five concurrents associated with other physical constants (20100320a_195-224). Similarly, when AB is asked to transform a letter into an italic font, instead a bold font is perceived (20100329_340-345).

Single inducer leads to multiple concurrents A single inducer may lead to the experience of multiple representations of the same concurrent. A letter or number may be directly induced but then the same concurrent may later simultaneously exist elsewhere in AB's experience, particularly if he is directed to perform some act upon that concurrent. For example, when AB is asked to view a four from a different angle, he reports to experience two fours, one in the normal (default), face-on view and one back-to-front (20100408_125-129). New or alternate representations of the same concurrent occupy different locations in the mental room. Multiple representations of the same fraction however (e.g. 1.5 and 1/2) tend to occupy the same space, with the new representation being "superimposed" on top of the old (20100229_24-25).

Concurrent experiences persist Once induced, the experience of the concurrent was found to persist without the need for it to be directly referred to. For example, AB reports that the concurrent "60 has rooted now because we've been talking about it for quite a bit" (20100229_329). Similarly AB reports that a percept may remain stable even if it is taken out of view or attention is directed elsewhere; once attention is returned, the concurrent is described as if it existed independently of AB's attention: "My view it went back to the 3. That's all still there as well. (20100229_388). INTERVIEWER: What if you... take them out of view completely... Do they remain exactly where they were before? AB: Yeah still five six, fifty seven." (20100305_131-132). This persistence of concurrents means that after several concurrents have been induced through the interview process, AB's experience contains multiple independent concurrent items, for example, "INTERVIEWER: Do you have any number line ready that we could do that with? AB: Erm, I've got all sorts of number lines." (20100408_386-387). This persistence in the visual representation and spatial location of a concurrent caused experimental difficulties where AB found there were too may concurrents present to concentrate on a single item, causing him to feel "bogged up with loads of numbers" (20100229_384).

2.4.3.3 Stability of percept

AB often reports 'instability' in his percepts, as a flashing or brief appearance of the concurrent. This instability is reported when AB attempts to modify a feature of the concurrent from its preferred or 'default' form. For example, attempting to change the typeface (20100329_340-345) or perspective of the alphabet form (20100415_97-113) results in an experience of a percept flickering between the default and requested view/feature.

AB has a concrete knowledge of where in space his concurrents are located (the defining feature of spatial sequence synaesthesia). This knowledge enables him to locate one concurrent with respect to another by directing his focus of attention to that space (20100329_254-255). Where AB's knowledge of a number sequence is limited (e.g. in the decimal places of pi), we find that he only experiences stable concurrents (i.e. with a temporal consistency in appearance of the singly induced item) for those numbers of which he is certain (20100229_132).

Selectively directing AB's attention to specific features of a concurrent appears to both improve the stability of the percepts and AB's ability to describe it, for example he often uses phrases such as, "if I think a little bit more then I see" (20100222_5) or "if I really try and focus" (20100229_398) before going on to describe a feature which was previously 'unstable'. Alternately this could be interpreted as directed attention changing the content of the experience rather than simply increasing the subjects access to the content. In either case, it appears that attention is able to selectively modulate the conscious visual content of the subject's synaesthetic experience.

2.4.3.4 Voluntarily controllable acts

AB is able to perform a number of acts to modify his synaesthetic experience. These include:

1. Changing perspective on a concurrent, either by physically moving around the room or adopting a different mental perceptual position such that he can view the concurrent from a different angle.

   INTERVIEWER: ...So how does it change when you stand up for example? AB: ...looks like I am kind of above it, kind of like this. It's kind of got some depth to it this time. (20100415_68-69)

   AB: And from my perspective now, four's kind of the wrong way round. Well I mean yeah, it's kind of sort of so it would be the right way round if I was standing sort of

over there, but the four's kind of there and I'm here. (20100222_303)

2. Self-induce concurrents by thinking about them, looking for them in relation to other concurrents or through the internal recitation of the concurrent (inner speech)

   INTERVIEWER: Can you create a different number line... Maybe over there for example, if you say 55 over in that direction... AB: I just faced this direction and then thought of 55. (20100305_135-142)

3. Overcome physical interference in the mental room through effortful 'willing' of the concurrent to appear.

   AB: Well it just appears first away from the [physically presented paper] page. I have to will an alphabet on the page in order to get it to happen. (20100408_75)

4. Report a visual memory of a concurrent without evoking the concurrent itself.

   INTERVIEWER: Did you notice any numbers when you came into this room? AB: No, erm maybe I can remember there was something here. ... Hard to tell if it's just a memory or if it's really there. INTERVIEWER: Well have a look at the wall. AB: I remember something being over there as well. Can't remember what number it was whether it was a 55 or a 56. Yes, so there's obviously nothing there that's sort of firm there. Kind of got a bit of an image of a big 55 there then a big 56 sort of stuck on the wall there. Nothing really that stable. (20100320a_2-9)

We also find that although AB's reports would suggest that he can in some cases modify a concurrent itself, attempts to do so lead to the generation of a new concurrent with the desired characteristic, whilst the original remains unchanged. Complete descriptions of all the themes deduced from this data, with examples, are provided in Appendix A.1.

2.5 Discussion

In this Chapter we use the EI technique to provide a detailed phenomenological analysis of SFS in a single case. The conclusions drawn are appropriate to our participant and further work will be required to demonstrate their applicability to a wider population. We are, however, able to perform some external validation of the themes derived, by reference to the existing (limited) descriptions of phenomenology. Where there is continuity between the reports of our participant with those provided elsewhere, we may assume that these particular themes are generalizable to a wider population. As our participant has been found to report similar phenomenological details in most aspects of their experience, particularly in the basic form descriptions, we may suggest that his experience in general is not atypical of a wider SSS population. Where other more novel aspects of phenomenology are derived for this participant, it is possible that these too may be generalizable.

Our results show that AB's synaesthetic concurrents exist in what he terms a 'mental room' and he is able to selectively shift his attention to either the mental room of the concurrents or the 'physical room' in which the interviews were conducted. Although the mental and physical rooms co-exist, percepts in the physical room appear to interfere with synaesthetic concurrents in the mental room. This interference effect was also found to be a feature of visually presented inducers such that AB had to divert his gaze from the physical inducer in order to perceive the concurrent. The generation of a concurrent was found to most frequently follow auditory induction, for example AB uses internal verbalisation of the inducer name in order to perceive the concurrent, even when it is presented visually. We also find that concurrents are automatically experienced by association to the inducer, for example the discussion of the physical constant for the speed of light causes the automatic perception of related physical constants. Here we also see that AB's concurrent are not limited to simple letters/numbers, but also include equations and graph notations such as . The induced item is also perceived with adjacent items on the number line, for example the induction of a 2 may lead to the automatic perception of a 1 and a 3. The stability of synaesthetic percepts is found to increase with focused attention, that is when AB reports to effort-fully spend time focusing on the concurrent percept. We also find that he is able to voluntarily modulate the features of a concurrent, although they appear to have a default typeface or perspective.

A number of themes relating to the presentation and experience of SFS can be derived from the interview sessions with AB. Some of these themes may be specific to AB, for example the experience of a 'black hole' associated with and representative of infinite

decimal places. However, others may also characterize the phenomenological experience of the wider SFS population. Examples of these themes are presented below in terms of emergent theories relating to the nature and development of the SFS experience. In many cases, our themes are validated by qualitative reports obtained by other means. Each of the themes or theories identified here could themselves be further investigated in a series of interviews over multiple subjects.

2.5.1 Physical-mental room

AB's description of the mental-room can be considered in light of the projector and associator distinctions in grapheme-colour synaesthesia (Dixon et al., 2004). AB reported in the first interview that he is "projecting a mental image" when he perceives a synaesthetic concurrent (20100215_22). AB's description of the mental room as in "another dimension" (20100408_185) is interesting, but of itself says little about the experience. More telling is the apparent relationships between the physical and mental rooms such that the physical can obscure or distract from the mental and make it difficult to visualise or fully induce a concurrent. We speculate that t hose synaesthetes considered to be projectors are those who experience little interference between the physical and synaesthetic.

2.5.2 Inner speech

We found that AB internally verbalised the name of the inducer each time he self-induced a concurrent (i.e. the inducer was not presented by the interviewer). This includes occasions where he redirected his attention from one concurrent to another or when he freely chose a concurrent to explore. We also found that when he was visually presented with an inducer, he needed to say the name of that inducer internally before the concurrent was experienced and repeated the name of the inducer to stabilise his visual experience and maintain his focus of attention. This use of inner speech was uniquely identifiable by the process of EI; other methods may have accepted AB's first level descriptions (e.g. of the redirection of spatial attention) without probing further into the acts involved in this process. This is an example of EI enabling reflective access to an aspect of subjective experience which was previously prereflective. this also exemplifies the in-depth exploration of diachronic structures of experience promoted by EI.

We found that external auditory instruction is the most direct or effective route to induction of a concurrent for AB. The primacy of auditory induction may account for AB's apparently persistent use of inner speech during all other inductions (we note however a

specific occasion where AB reported to "envision" an inducer in order to experience the concurrent (20100222_261-263)). Auditory-visual synaesthesia is commonly considered to include only more overt forms such as the experience of colours with music. As such, SFS and other forms (e.g. grapheme-colour synaesthesia) have typically been assumed to result from visual-visual interactions as both modalities. There are however investigations of visual-visual types which have used auditory presentation of inducers and found results comparable to visually presented inducers (Nunn et al., 2002; Paulesu et al., 1995; Steven, Hansen, & Blakemore, 2006). In SFS, a case has also been described in which auditory and visual presentation of an inducer lead to different perspectives of the form being perceived (M. Jarick, Dixon, Stewart, Maxwell, & Smilek, 2009). These findings suggest that auditory induction is necessary and sufficient to cause the synaesthetic experience, and the evidence here from EI suggests that it is in most cases necessary.

Assuming there is some overlap between the neural mechanisms involved in processing internal versus external speech (with the notable exception of self-monitoring processes involved during inner speech (Simons et al., 2010)), the processes of current induction via inner speech may be similar to the process involved in in concurrent induction via external auditory presentation. As all methods of induction engaged inner speech for this subject, the experience of SFS might be re-framed as primarily auditory-visual process for AB and potentially in other SF synaesthetes. Compatible with this hypothesis, children in most English-speaking countries learn the ordinal sequence of the alphabet phonemically through song before they are able to associate the visual grapheme and letter name (Ehri, 2009). Seron et al. (1992) found that the SF synaesthetes they investigated were less efficient in verbal strategies according to Paivio's degree of imagery questionnaire (Paivio & Harshman, 1983) and suggest that the visual spatial form may have developed as a compensatory strategy to reinforce the ordinality of audibly presented items (Seron et al., 1992). This suggestion may have particular implications for the development of SFS, particularly if it is framed as an auditory-visual association, rather than a visual-visual or visual-spatial.

2.5.3 Visuospatial memory and persistence of concurrents

We found that once induced, a concurrent will continue to be experienced even when direct attention is drawn away from it. Similarly, Jarick reported that his subject (L) experienced a persistence of induced concurrents until they were "not needed any more" for the purposes of mental viewpoint navigation (M. A. Jarick, 2010, p88). We also find

that AB experiences a sense of 'presence' when he cannot directly see a concurrent but knows where it should be in relation to others. These two features suggest involvement of visuo-spatial memory processes in SFS, where the memory of a concurrent position is sufficient to hold the synaesthetic experience in active working memory, either as a visual experience or as non-spatial visual content. Brang et al. (2010) and Simner et al. (n.d.) have reported superior visuo-spatial memory abilities in SF synaesthetes, as demonstrated in their ability to learn new spatial forms (Brang et al., 2010) and perform above average in assessments of visuo-spatial recall such as the Visual Patterns Test (Della Sala, 1997; Simner et al., n.d.). Further investigation is required to demonstrate how this superior visuo-spatial memory translates into the experience of the concurrent itself, however our phenomenological data suggest that such investigations should be conducted with awareness that previously induced concurrents may continue to exert a spatial cueing effect on future trials.

2.5.4 Blind analysis retrodicts and amplifies previous spontaneous introspective reports

Analysis of interview data was conducted blind in order to limit the impact of interviewer expectancy effects on the conclusions drawn. There remains however a possibility that the analyst themselves introduced bias in interpretation, therefore further cross-validation may be required to examine the extent of analyst expectancy. For example, a second or third analyst would be required to inspect the data at a given level (e.g. at the level of theme generation, coding and aggregation, or summarising into theme descriptions) with a degree of agreement calculated between analysts taken as a measure of reliability. It is likely that analysts with differing levels of familiarity with the research topic will interpret the data differently. In the present investigation, it was intended by design that the analyst should have limited expert knowledge about the topic of SFS, such that the conclusions reached could be reliably derived by non-experts. Wider analysis of the data has been made possible by the publication of the raw and analysed interview data, and an open invitation for expert opinion (Gould, Froese, Barrett, Ward, & Seth, 2014).

The extent of analyst expectancy effects may also be assessed with reference to existing literature and the degree of support for the conclusions drawn. In the present investigation, reliability has been demonstrated by comparison to existing knowledge on the phenomenology of SFS, and the successful replication of aspects of the SFS experience which have been highlighted by previous research. Uniquely, however, such aspects

have been reported with a significantly greater level of detail (Gould et al., 2014). For example, 19 of the Seron et al. (1992) subjects report that once activated, a concurrent could not be moved, supporting our findings on the persistence of concurrents and AB's necessity to generate a new representation of the concurrent rather than modifying an original. Subjects also reported being better able to 'make use' of their representation where they had a free "visual field", e.g. when their eyes were closed. This statement is compatible with our findings of physical interference, where AB's concurrents were placed in areas of an uninterrupted visual scene in the mental room so as to avoid conflict with items in the physical room which hold more salience than the mental room concurrents. As with our subject, Seron et al. (1992) also report that for his subjects the "vividness" of the number concurrent increases when the subjects concentrate on it (Seron et al., 1992, p174). Through the application and analysis of the EI data collected here we have been able to identify that this concentration is experienced by the subject in many cases as internal recitation of the inducer name, highlighting the importance of inner speech in the induction process. Finally, one of Seron et al. (1992) subjects also reports to automatically experience the concurrents immediately surrounding the induced item, as with our subject.

2.5.5 New insights may be used to direct future qualitative and quantitative investigations.

The present findings suggest new opportunities for development in future investigations of SFS and associated synaesthesia phenomenology. For example, investigations should consider the potential for interference of physical objects in the perception of synaesthetic concurrents and associated limitations of visually presented inducers.

Earliest self-reports from SF synaesthetes described the experience as occurring involuntarily, automatically and without any conscious effort or awareness whenever an individual saw, heard or thought of an inducer (Cytowic, 1989). However, our subject anecdotally reports that he is not continually swamped with concurrents on a daily basis, despite continually reading and seeing numbers and letters in his external environment. For AB, the perception of a concurrent then is not entirely automatic, in line with evidence that automaticity of concurrents can vary in grapheme-colour synaesthesia (Rothen, Tsakanikos, et al., 2013). For our subject, the concurrent was generated through internal verbalisation; it remains to be seen, with the further application of EI or other procedures, how much further apparent automaticity of concurrent perception can be unravelled and

what effects this may have on future research endeavours.

The phenomenology presented here is by no means exhaustive of that which could be obtained by further EI and quantitative investigation. A number of unresolved issues are immediately identifiable, such as the role of inner speech and focussed attention in stabilising a concurrent. We may seek to establish how inner speech impacts mental imagery, and whether non-synaesthetes they employ similar methods of inner speech as observed here. We also note that, to the best of our knowledge, this is the first reported case of SFS in which a static visual scene is experienced as a concurrent. The incidence of this would be determined in other known synaesthetic and non-synaesthetic populations and assessments of consistency and automaticity made in order to determine if this qualifies as a new type of synaesthesia. We also demonstrate that the apparent automaticity of SFS can be investigated with this method in terms of phenomenological experience. Price and Mattingley (2012) have recently argued that SFS does not meet the necessary behavioural criteria to be termed truly automatic. Indeed, we have determined here that although synaesthetic concurrents were initially described to arise automatically, in the majority of cases, this subject went through a process of internal verbalisation of the inducer name before the concurrent was perceived. This may relate to the task-specific strategies suggested by Price and Mattingley (2012) to mediate the cueing effects of SFS. Further exploration of the diachronic and synchronic structure of the spatial cueing effect may determine the causal relationship between the appearance of the concurrent and the shift in spatial attention.

Further quantitative investigations could also be used to objectively validate the themes identified. For example, the physical interference effect could be investigated through the use of interactive virtual reality and a recording of participant 'placement' of concurrents. Subjects such as AB appear to have difficult experiencing concurrents where their visual scene also includes veridical percepts. We would then predict that the placement of a concurrent should be away from veridical percepts. Virtual reality could be used to manipulate the placement of veridical percepts, with the participant interacting with the environment (through a joystick or other device) to identify where there concurrent is located. We would predict that the degree of physical interference may vary across the population, and thus that continuous patterns in the spatial distribution of concurrents from veridical percepts may be observed. Alternatively, this variation may cluster into distinct groups, such as who experience no interference and those whose concurrents are placed maximally distant from veridical percepts.

Another aspect which could be amenable to quantitative investigation is the hypothesised use of inner speech in concurrent generation following visual presentation. Event related potential (ERP) studies have previously demonstrated that an N1 component is generated by the superior temporal gyrus of the auditory cortex in Response to auditory stimuli of all kinds, including inner speech (Ford, 2001). The detection of an N1 superior temporal gyrus component following visual presentation of inducers would be evidence of the involvement of auditory structures in the production of synaesthetic concurrents. Such an experiment may require an explicit instruction to the synaesthetic participant to focus on and attend to the concurrent generation. It is likely however that visual presentation of inducers similarly activates auditory cortices in control subjects, if they are not explicitly instructed to avoid inner speech. The observation of greater consistency of this component in synaesthetes compared to controls following visual presentation may however be suggestive of increased propensity for inner speech in concurrent generation. A causal relationship between inner speech and concurrent generation could be investigated through the interruption of speech processes via rTMS, and a subsequent reduction in the directional cueing effects reported in behavioural studies of SFS. A recent review of TMS in the investigation of speech process has highlighted the value of this method in disambiguating the roles of the implicated sensory and motor systems (Murakami, Ugawa, & Ziemann, 2013). Further consideration would be needed to determine which aspects of the speech system would be most appropriately targeted to reduce the effectiveness of inner speech production in synaesthetes prior to concurrent induction.

2.6 Conclusions

Phenomenological descriptions of spatial form synaesthesia (SFS) have so far been largely confined to descriptions of spatial locations (concurrents) pertaining to specific inducers (e.g., numbers, letters, calendar date). Here, employing a second-person method designed to increase the reporting access to pre-reflective aspects of experience, we have provided a comprehensive description of our subject's spatial form for a range of ordinal sequences including number, calendars, alphabets and ages, dramatically extending phenomenological descriptions of SFS or indeed any other form of visual synaesthesia. We also introduced new associated synaesthetic experiences such as concurrents for graphs, equations and mathematical concepts. Using the formalism of Grounded Theory analysis, we identified seven main themes in AB's SFS experience, as below (items marked $*$ have not been discussed here. For further information these items, please see Appendix A.1). These themes

have not been described elsewhere with to a significant level of detail in the phenomenological experience. Here we have demonstrated that not only is it possible to gain reliable and informative second-person descriptions from nave subjects, if data collection and analysis proceed in an informed and rigorous manner, and that qualitative investigations of this sort can be of value to future quantitative investigations.

1. Form descriptions
2. Physical and mental rooms
3. Inducer-concurrent relationships
4. Stability of the percept
5. Voluntarily controllable acts
6. Perspective taking on the concurrent∗
7. Concurrent contexts∗

We report here the first application of the EI method to SFS and indeed to synaesthesia more widely. In doing so, we have gained unprecedentedly detailed information regarding the precise phenomenology of this subject which may be generalizable to a wider population. We have also provided access to interview data in its structured and analysed form. This is a rich data source and we invite the interested reader to explore avenues for further connections between the themes uncovered here and other aspects of SFS, or synaesthesia more generally, which may be of relevance to understanding these phenomena. We have demonstrated that the EI technique can be usefully applied to explore synaesthesia phenomenology and we propose that these findings may guide future qualitative research. Such appreciation for the precise phenomenological experience in synaesthesia may focus future research endeavours, as we seek to understand the extent and limitations of the experience from the perspective of the participant.

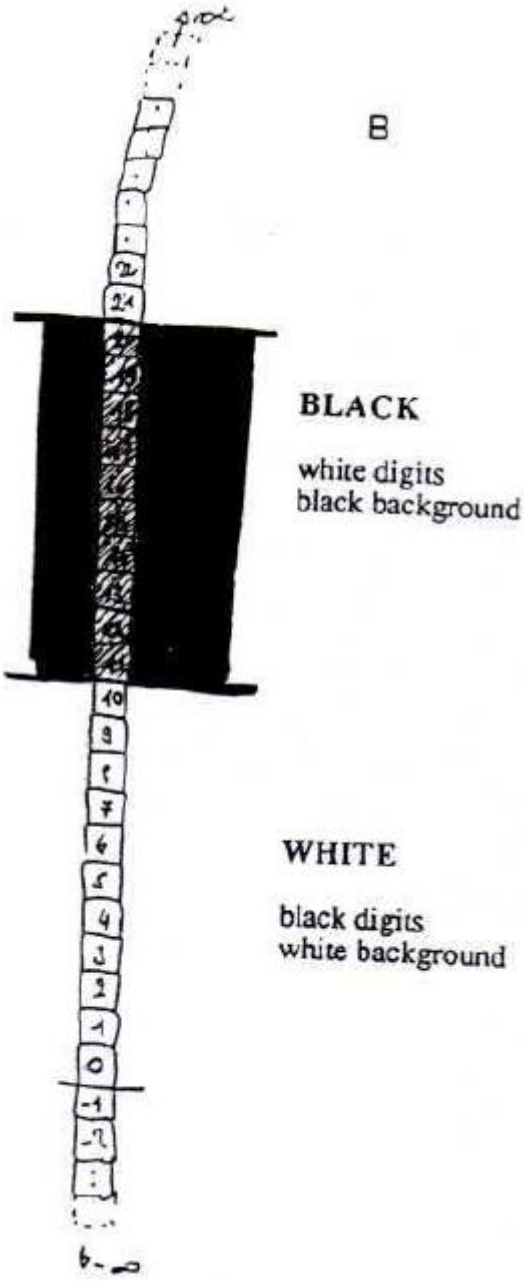


Figure 2.4: Number form for subject JB reported in (Seron et al., 1992). Note the features of defined background colour, similar to the context reported by our subject, and the high contrast between digit and background colour, which we propose to be a feature of the context, enabling the concurrent to be readily visible.

Chapter 3

Colour area activation in grapheme-colour synaesthesia

3.1 Chapter summary

This Chapter addresses debates in fMRI investigations of grapheme-colour synaesthesia (GCS), in which letters and numbers are associated with the concurrent experience of colours. We present an fMRI investigation of a large ($n = 20$) and representative GCS sample and compare activation with matched controls ($n = 20$). We specifically address the debate regarding colour area activation during synaesthetic colour experiences, which is not fully replicated across different studies. We hypothesise that individual differences in synaesthesia phenomenology modulate the degree of colour area activity, such that synaesthetes with more highly localised concurrents would demonstrate greater activation in colour-selective areas, as previous successful replications of colour area activation have primarily used subject groups which contain a large proportion of 'projector' synaesthetes.

An independent colour area localiser was used to determine colour-selective ROIs on a participant-by-participant level. Regression analysis was conducted between BOLD activation in colour-selective ROIs under synaesthetic conditions and individual CLaN-Localisation scores. In exploratory analysis, regression was also conducted against the newly defined phenomenological variant of synaesthesia attention and automaticity (CLaN-A). We also explored the influence of these two phenomenological factors at a wider level, through whole brain regression.

Individual differences in localisation and automaticity we found to significantly predict the degree of response in colour-selective ROIs under synaesthetic conditions, with left colour areas modulated by localisation and automaticity and right colour areas modulated by localisation alone. We also find a number of other areas to be modulated by GCS phenomenology, including the opercular part of the right inferior frontal gyrus in relation to automaticity of synaesthetic concurrents. These results are the first demonstration that colour area activity in GCS is affected by individual phenomenology, and are in agreement with previous investigations when sample populations are assessed for projector-associator differences. We propose that future investigations of GCS account for the effects of individual differences through regression analysis using the localisation and automaticity measures applied here, in order to more effectively characterise the neural underpinnings of the trait.

3.2 Introduction

3.2.1 fMRI investigations of grapheme-colour synaesthesia

The perceptual nature of GCS was afforded significant support by the experimental demonstration that in at least some synaesthetes, the concurrent colour experience was associated with increased BOLD activation in areas of the brain relevant to processing physical colour, specifically V4 (Hubbard & Ramachandran, 2005; Nunn et al., 2002). Since this early work, a number of other investigations have similarly concluded that the topographical brain response to synaesthetically induced colour is similar to the response to physical colour (e.g. (Gray et al., 2006; Sperling et al., 2006; Weiss & Fink, 2009; Weiss et al., 2005)). A number of areas have been shown to be consistently reproduced in fMRI investigations of GCS, including bilateral ventral-occipital areas, the superior and inferior parietal lobes, bilateral insular, the left precentral gyrus and areas of the frontal cortex (see Rouw (2011) for a review). These activations have been proposed to support different roles in the generation of synaesthetic concurrents, with the parietal activation related to binding of the synaesthetic colour and veridical letter, the insular cortex activation reflecting the affective response to concurrents, the precentral response relating to interaction with the external environment and the frontal cortex activation demonstrates the cognitive control required in simultaneous processing of a synaesthetic and physical colour experience (Rouw, 2011).

The activation of real colour areas in GCS has not been systematically replicated, however, (e.g. Gray et al. (2006); Rich et al. (2006); Rouw and Scholte (2007)), leading Hupé and colleagues to emphatically state that "the neural bases of grapheme colour synaesthesia are not localized in real color sensitive areas" (Hupé, Bordier, & Dojat, 2012, p. 1622). In a review of synaesthesia fMRI investigations, Rouw et al. (2011) report that only five out of the 12 studies included identified V4 proper activation in response to synaesthetic colour (two in whole brain analysis, three in ROI). The authors suggest that methodological differences in task and analysis are possible sources of the variation in replication of this key result. For example, as Rouw et al. (2011) point out, not all investigations have applied retinotopic mapping and therefore any conclusions drawn in these papers cannot be explicitly linked to V4 activation proper. It is worth remembering however that in the original demarcation of V4 as a 'colour sensitive area', Zeki and Marini suggest that V4 is but one of the areas in a distributed network which supports colour processing (Zeki & Marini, 1998). This suggests that perhaps we should not draw too heavily on the precise topographical localisation of V4 as the prime colour selective area. As suggested by Rouw et al. (2011), we may instead apply independent colour area

localisation in order to identify colour selective areas.

Until recently, little attention has been focused on the impact of individual differences in fMRI analysis (see however Rouw and Scholte (2007); van Leeuwen, den Ouden, and Hagoort (2010)). Rouw et al. (2011) suggest that individual differences in synaesthetic experience will likely adversely affect population level inference statistics, particularly in small populations, and advise that future investigations should select synaesthetes based on characteristics of their experience, "e.g. strong perceptual sensations" (ibid. p.224). It is likely that the phenomenological heterogeneity of synaesthesia is a reflection of the neural heterogeneity in the expression of this trait, thus it may be more informative to include a wide variety of subjects and control for the effects of individual differences with appropriate regression analysis. Without controlling for individual differences, it may be inappropriate to generalise the results from small sample populations to the wider GCS population, and we may report greater inconsistencies in results. Presently, differentiation based on individual phenomenology is largely limited to categorical projector-associator (PA) distinctions, that is, the extent to which synaesthetes report their concurrents to be experienced with some external reference from (projector synaesthetes) or as more of a loose association with no externalised experience (associator synaesthetes). We note however that binary categorisation of groups, such as projector or associator, yields reduced statistical power compared to continuous measures, thus categorical subgrouping may impede our ability to detect significant effects at the group level.

3.2.1.1 Projector and associator fMRI findings

The PA dichotomy is not agreed upon by all authors (e.g. Edquist et al. (2006); Ward et al. (2007)), however investigations which employ these categorical distinctions have provided empirical support for underlying neurological differences between the basic categories of projector and associator synaesthetes, particularly in relation structural and functional differences in theories of concurrent induction. For example, Rouw and Scholte's (2007) investigation of structural differences in synaesthesia demonstrated that projectors were found to have greater fractional anisotropy (FA) in the right temporal inferior cortex, suggesting an increase of local connectivity in this area in projectors compared to associators. In functional imaging, the same synaesthetes viewed stimuli designed to evoke three different levels of synaesthetic experience (strong, weak and none) and were required to press a button with every trial contingent on the font (italicised or not) of each stimulus. Despite differences in FA between projectors and associators, Rouw and Scholte found

no PA related BOLD differences in any of the areas relating to the synaesthetic colour experience (frontal cortex, cerebellum and fusiform gyrus). Thus although the PA measure may highlight structural differences, it was not sensitive enough at this sample size ($n = 18$)to identify differences in activation which are believed to be related to the visual synaesthetic experience. This finding may be suggestive of the limitations in dichotomous PA split to fully describe the individual differences in synaesthetes, as it was designed based on differences in the visual experience and yet no differences in visual processing were found. In an extension of this study (with a sample size increased from 18 to 42 synaesthetes) Rouw and Scholte reported increased parahippocampal BOLD signal and increased GM in the hippocampus and angular gyrus of associators (Rouw & Scholte, 2010). The authors suggest that the hippocampal involvement is related to the 'internal' experience of associators, who generally describe their experience as existing in the 'mind's eye' as opposed to in some external reference frame. The authors conclude by likening the associator experience to retrieving a memory "whereas the projector experience more closely resembles perceiving of and acting in the outside world" (Rouw & Scholte, 2010, p. 6211). This is an intuitive metaphor, however the between subject contrast which identifies the associator parahippocampal activation ("associators and controls > projectors" (Rouw & Scholte, 2010, table 3) could alternatively be interpreted as evidence that projectors showed decreased activation relative to associators and controls, suggesting that the projector experience alone is differentiated from controls in this task and not segregating both projector and associator synaesthetes from controls, as would be expected. The inclusion of the control group in this between group comparison suggests that associators exhibited a more normal level of hippocampal activity (not different from controls) when engaging in the grapheme perception task, whereas projectors exhibited significantly less hippocampal activity than normal. The finding here of decreased parahippocampal activity in projectors may then suggest that they employ less memory related functionality in the execution of this task relative to associators or controls (see Rothen, Meier, and Ward (2012)) for a review of the interaction of synaesthesia with memory functions.

Elsewhere, Van Leeuwen and colleagues have investigated differences in functional and effective connectivity between projectors and associators[1]. van Leeuwen et al. (2011) reported that the degree of superior parietal lobe (SPL) activation differs between projectors and associators in a response to inducers (without contrast to other conditions), with associators showing increased SPL activity compared to 'mental screen projectors'

[1]This topic will be addressed further in Chapter 4

(van Leeuwen, Petersson, & Hagoort, 2010)[2] (van Leeuwen, Petersson, & Hagoort, 2010). van Leeuwen et al. (2011) proposed that associators are required to build two spatial reference frames, one for the concurrent and one for the external stimulus, thus the dual nature of the inducer and concurrent experience requires switching between these reference frames and increased difficulty in spatial binding. This increased binding is suggested to be evident in increase in SPL activation.

Where individual differences in PA phenomenology have been included in investigations of colour area activity, the data suggest that significant colour area activation is more commonly reported in sample populations which contain a higher proportion of projectors relative to associators. For example, Rouw and Scholte (2007) report a group difference in activation (synaesthetes > controls) in the right fusiform gyrus in response to inducing > non-inducing graphemes. In this sample population, approximately 40% of the synaesthetes score as projectors on the PA questionnaire. The authors do not imply that this fusiform activation is in the area of V4, however, elsewhere this finding is taken to support claims of V4 activation to synaesthetic colour (e.g.Hubbard, Brang, and Ramachandran (2011)). We note that although the FG activation of Rouw and Scholte (2007) is more lateral than previous localisations of V4, it is very close in both the anterior-posterior and dorsal-ventral directions. As noted previously, colour-selective activation is not limited to V4 (Beauchamp, Haxby, Jennings, & DeYoe, 1999; Zeki & Marini, 1998) and as independent colour area localisation was not performed in the investigation of Rouw and Scholte (2007), we cannot conclusively reject the hypothesis that this cluster does indeed reflect the 2nd level localisation of a colour-selective response. On the assumption that this is indeed a colour selective response, this finding is suggests that inclusion of a large proportion of projectors relative to associators will lead to colour area activation, particularly in the right hemisphere.

Projector-associator information is also provided in (van Leeuwen, Petersson, & Hagoort, 2010), where a group difference in activation (synaesthetes > controls) in the right fusiform gyrus was identified in ROI analysis of inducing > non-inducing graphemes. No main effect of projector-associator subgrouping was found in relation to the response magnitude in the fusiform gyrus, however, this difference may be attributed to the use of categorical rather than continuous measures of phenomenology. The synaesthetic participants included in this study were seven projectors, seven 'mental screen projectors' and five associators. The inclusion of this additional sub-group of mental screen projectors

[2]The classification of 'mental screen projector' is unique to this investigation. The authors described these individuals as experiencing the concurrent in external space but not on the grapheme itself

complicates the interpretation of the result, however if they might be termed 'projectors' this again suggests that a high proportion of projectors in this sample (67%) may be in part responsible for the significant right fusiform gyrus activation to synaesthetic colour.

3.2.2 A new phenomenological measure: The Coloured Letters and Numbers questionnaire

The Coloured Letters and Numbers (CLaN) questionnaire was developed by Rothen, Tsakanikos, et al. (2013) to assess sources of individual differences in synaesthetic phenomenology which are reported anecdotally but have not been explored experimentally. Such facets include the vividness of the synaesthetic experience, and the relative automaticity of the colour experience. Rothen, Tsakanikos, et al. (2013) hypothesised that formal investigation of such individual differences may contribute to our understanding of performance in behavioural or cognitive tasks, over and above the categorical projector-associator distinction. Following data collection in an extended population of 628 grapheme-colour synaesthetes, and rigorous statistical analysis appropriate for the validation of new questionnaire methods, four distinct factors emerged:

1. **Localisation** - the location of the synaesthetic experience with higher scores denoting a tendency to see colours that are located.

2. **Automaticity** - aspects of automaticity and attention of the synaesthetic experience with higher scores indicating greater automaticity and less attention to the inducing stimulus for the synaesthetic experience to be elicited.

3. **Deliberate Use** - deliberate use of synaesthetic experiences in everyday life with higher scores indicating increased usage of synaesthetic experiences in everyday life.

4. **Longitudinal changes** - longitudinal changes of synaesthetic experiences with higher scores indicating that the synaesthetic colours changed intensity over time.

The localisation factor (CLaN-L) is reported to be conceptually related to the projectorassociator distinction, although it may not be identical to it. For example, in the standard view, a projector is classified as one who experiences the synaesthetic colour to have an external reference frame, but externalisation of a concurrent is not a necessary feature of CLaN-L, indeed a participant may report to have a specific location for their concurrent experience, but that location may be 'in the mind's eye'. Rothen, Tsakanikos, et al. (2013) also note that a standard associator experience does not accord with a low CLaN-L score,

as questions relating to an associator-like experience, such as claims to know but not see synaesthetic colours do not load onto the same CLaN-L factor. Thus it appears that although there is similarity between CLaN-L and the projector-associator dichotomy, they do not describe the same phenomenological experience and thus cannot be treated as equivalent. This factor may be of particular importance in fMRI investigations of GCS as it relates to the vividness of the synaesthetic experience. In memory research, the vividness of a memory has been related to the degree of activation in hippocampal areas during both encoding and retrieval (Wais, 2008). We might then hypothesise that a vivid or localised synaesthetic colour experience would be associated with a greater degree of activation in colour areas, as compared to a non-localised synaesthetic concurrent.

The automaticity factor delineates synaesthetes on the degree to which they report concurrents to be experienced automatically or with little attention afforded to the inducing stimulus. Accordingly, those participants who scored high on this factor also experiences less Stroop interference in a synaesthetic colour naming task. In the classical definition of synaesthesia, concurrents are experienced automatically, and yet the CLaN analysis demonstrated that the degree of automaticity of the concurrent experience is variable across a population. As this is a relatively unexplored aspect of synaesthesia phenomenology, it may be difficult to ascribe a specific neural hypothesis to the phenomenological variation, however it is likely these differences may be observed in differential activation of frontal areas normally associated with attentional processes (see for example Stuss (2006)).

3.2.3 Aims of the present investigation

The key finding of colour area activation during the synaesthetic colour experience has not been widely replicated, but it appears that where colour area activation is reported, the participant groups are comprised of a relatively high proportion of projector synaesthetes relative to associator synaesthetes. Although this is informative, the dichotomous characterisation of synaesthetes as either projector or associator limits our ability for wider interpretation of data from a heterogeneous sample population. We hypothesise that a continuous measure of synaesthetic phenomenology will enable a more precise investigation of the variation in colour area activity, and propose that the newly developed CLaN localisation factor may be suitably employed in this regard. Specifically, we hypothesise that those synaesthetes who report highly localised concurrents will demonstrate a greater degree of colour area activation then those with less localised concurrents, and that such a relationship may be demonstrated by regression of individual levels of BOLD activation

in colour selective areas with individual differences in CLaN-L. This is in accordance with memory literature, where the degree of hippocampal activation has been demonstrated to be related to the vividness of the reported memory. Importantly, we will not rely on the topographical or retinotopic location of BOLD activation to infer true colour area activity, as colour selective activity has been demonstrated to include areas other then retinotopic V4. We will therefore use an independent colour area localiser to identify colour selective areas on an individual participant level, and use these areas in the investigation of colour area responses during the experience of synaesthetic concurrents. Prior to testing the validity of our hypothesis, we will first investigate the group level effects to demonstrate that our group as a whole expresses regional activation which is consistent with the existing synaesthesia literature, including a brief statement regarding our group composition hypothesis on group level colour area activation, where we predict that group level activation at the whole-brain or ROI level will only be evident in sample populations containing a high degree of projector synaesthetes. We will then investigate the effects of individual differences in localisation on colour area activation under synaesthetic conditions.

We also take the opportunity to explore the phenomenological variation in automaticity of synaesthetic concurrents (CLaN-A). As this is a novel application of this measure of phenomenology to neural data, we hold no specific hypotheses regarding the interaction between automaticity and regional brain activation and how these relate to the individual synaesthetic experience. It is predicted, however, that the automaticity of synaesthetic concurrents may be related to activation in frontal areas normally associated with attentional processes, and potentially also in colour area activity. This relationship will be investigated through regression analysis of whole brain activation during synaesthetic conditions, and also through regression of activation in colour selective areas against individual CLaN-A scores. We also explore the whole brain effects of differences in CLaN-L, to determine whether there are regional effects outside of the predicted colour-selective areas.

To the best of our knowledge, there have been no reported investigations of veridical colour processing in synaesthetes compared to controls. This may be surprising given the demonstration that synaesthetes exhibit increased acuity in colour discrimination, evident in significantly improved performance over controls in the Fansworth-Munsell Hue (FMH) test (Banissy, Cohen Kadosh, et al., 2009; Yaro & Ward, 2007). Despite the suggestion that synaesthetes do no exhibit generalised differences in colour processing (Hubbard et al., 2011), this result in the FMH test suggests that there are indeed differences in

the processing, the result of which is increased acuity in colour discrimination and possibly sensitivity. Although no assessment has been made regarding individual differences in FMH performance and colour area activation, the reduced V4 activation reported in patients with achromatopsia compared to controls (for a review see Bouvier and Engel (2006)) may lead us to tentatively suggest that increased V4 activation may be correlated with increased accuracy in the FMH test. We will also therefore conduct an exploratory analysis of individual differences in activation in veridical colour processing through whole-brain regression of the contrast used to identify colour processing areas and the phenomenological variables of CLaN-L and CLaN-A, in order to investigate the differences in performance between synaesthetes and controls in veridical colour tasks.

3.3 Method

3.3.1 Participants

The conduct of this project was approved by the Research Governance and Ethics Committee for Brighton and Sussex Medical School (Project Approval Reference: 10/049/GOU). All volunteers took part in pre-screening for MRI safety, reported no history of physiological or psychological trauma and normal colour vision. Control participants additionally reported no synaesthesia of any form for themselves or up to 2nd degree relatives. 20 grapheme-colour synaesthetes (age 18-56 years, mean age 28.45 years; 13 female; 16 right handed) and 20 controls matched for age, gender, handedness and education level (age 19-52 years, mean age 28.5 years) were recruited through local advertising and via the synaesthesia database established at the University of Sussex.

3.3.2 Eagleman battery

GCS was confirmed in synaesthetic subjects through completion of an online synaesthesia battery (Eagleman et al., 2007). This battery consists of a synaesthetic concurrent consistency test and a speeded congruency test. The consistency test aims to establish test-retest reliability in the selection of synaesthetic colours for individual concurrents. Subjects are presented with the numbers 0-9 and letters A-Z three times each in a randomised order. To each presentation, subjects are required to select their concurrent from an array of 256 x 256 x 256 colours (see Figure 3.1). Upon competition of the battery, the RGB values of the concurrents selected for each trial are made available to the researchers for the production of experimental stimuli. Internal consistency, i.e. consistency in concurrent selection for each presentation of the grapheme, is calculated as the geometric distance in RGB space between the three trials for each grapheme. The total distance for each subject is then normalised by dividing by the total number of graphemes tested, providing a total consistency score for that participant. The consistency scores are used to qualify a subject as synaesthetic, where non-synaesthetic participants typically show far less consistency in concurrent colour selection, even with the use of memory aids. Based on data obtained in the development of this test, a consistency score of ≤ 1 is classified as synaesthetic, although the authors state that this threshold represents an "optimal divide" between the synaesthetic and non-synaesthetic populations, rather than an exact cut-off (Eagleman et al., 2007, p. 141). The thresholds for the determination of colour consistency in GCS have recently been explored by Rothen, Seth, Witzel, and Ward (2013) and it has been demon-

strated that a cut-off of 1.24 achieves optimal specificity and sensitivity in distinguishing synaesthetes from controls. Rothen, Seth, et al. (2013) additionally suggest a CIELUV transformation of RGB values to more appropriately model perceptual colour space than RGB distances and find that a CIELUV threshold of 135 achieves optimal specificity and sensitivity in this regard.

The speeded congruency test of the Eagleman et al. (2007) battery measures reaction times of participants in the identification of inducer-concurrent pairings as congruent or incongruent to their synaesthesia. Here, each grapheme identified as an inducer for that participant is presented for 1 second. In 50% of the trials the grapheme is presented in its congruent colour, as identified in the consistency test. In the other 50 % of trials, the grapheme is presented in the congruent colour of a different grapheme, thereby an incongruent for this grapheme. The user identifies the presented colour as congruent or incongruent by a button press of options "It matched [my synaesthetic colour]" or "It didn't match [my synaesthetic colour]" the synaesthetic colour (see Figure 3.2). Eagleman et al. (2007) report that synaesthetes score an average of 94% accuracy in correctly identifying their own concurrents and reaction times of 0.64±0.78 seconds whilst non-synaesthetes score 67% accuracy and reaction times of 0.91±0.87 seconds. In this way, the speeded congruency scores are used to additionally qualify the participant as synaesthetic or not when compared to the distribution of scores from a self-identified non-synaesthetic population.

Inclusion criteria for synaesthetic subjects were significant evidence of the GCS trait based on the consistency score (CIELUV transformed) and speeded congruency results of the Eagleman battery. Additionally, each subject was required to have a six different letter-colour pairs suitable for experimental stimuli. Letters were selected for which the participant scored the highest consistency in concurrent selection (least distance in RGB space between successive selections of concurrent colour) and which provided a variety of colours, excluding black or greyscale items, or those which had low contrast against the grey isoluminant background screen.

3.3.3 Synaesthesia phenomenology questionnaires

Synaesthesia phenomenology was assessed by the Illustrated Synaesthesia Experience Questionnaire (ISEQ) (Skelton et al., 2009) (see Appendix B.1)), Rouw and Scholte's Projector-Associator questionnaire (RS-PA) (Rouw & Scholte, 2007) (see Appendix B.2) and the newly developed Coloured Letters and Numbers (CLaN) questionnaire (Rothen, Tsakanikos, et al., 2013) (see Appendix B.3). The ISEQ and RS-PA contain 5 and 12 items

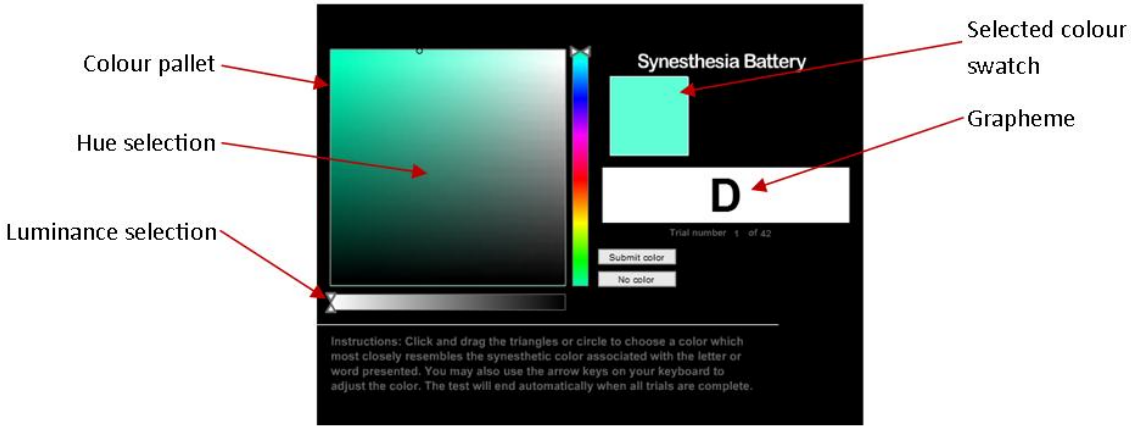


Figure 3.1: Screen shot of the colour consistency test from the online synaesthesia battery (Eagleman et al., 2007). Users are instructed to select the colour from the palette which most closely resembles their concurrent for the presented grapheme (e.g. in the above "D"). The hue of the colour palette is altered with the vertical slider and the saturation and luminance by the position of the cursor on the main palate. The selected colour is displayed in a swatch above the grapheme. Users also have the option to select "No color" for the grapheme if that item does not have a concurrent. Clicking "Submit color" or "No color" progresses the programme to the next trial.

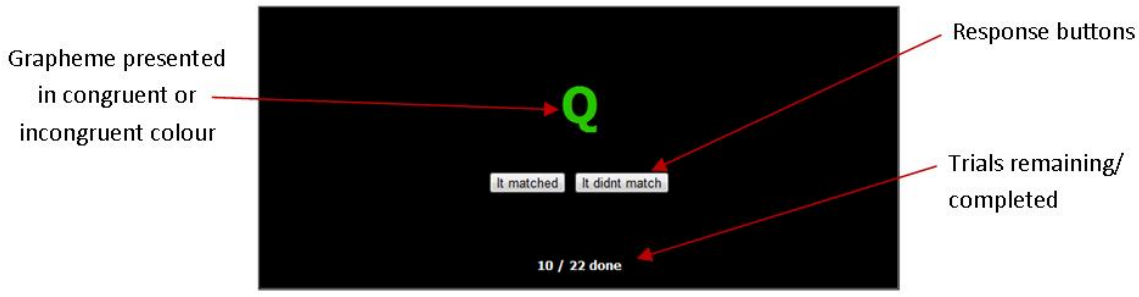


Figure 3.2: Screen shot of the speeded congruency test from the online synaesthesia battery (Eagleman et al., 2007). Users report whether the veridical colour of the grapheme "matched" (left button) or "didn't match" (right button) their synaesthetic colour for that grapheme. Graphemes are displayed for 1 second only. Reaction times are calculated from the user's system clock and expected to be accurate within a few milliseconds. Reaction time and response accuracy are presented to give a combined speeded congruency score.

respectively, addressing the projector-associator dimension of the synaesthetic experience. In both measures, participants rate their experience on a Likert scale of "strongly agree" to "strongly disagree" to questions such as "It seems that the colour is on the paper where the letter/number is printed." (Rouw & Scholte, 2007). Questions describe typical projector-like or associator-like experiences such that the final score for the participant can be taken as a difference between their combined ratings for the projector questions minus the associator questions. On the RS-PA a total difference score of > 0 is classed as a projector whilst a score of < 0 is an associator. The ISEQ similarly qualifies < 0 as an associator but defines those scoring between 0 - 1.05 as "undetermined" whilst score >1.05 is classed as a projector.

The CLaN questionnaire contains 30 items addressing numerous aspects of the synaesthetic experience, including automaticity and attention, variability of the concurrent experiences over time, deliberate use of synaesthesia in every day experience and location and typification of the experience in the projector-associator dimension. Questions are answered against a Likert scale of "strongly agree" to "strongly disagree". Questions relating to individual factors are clustered and a total for that factor determined. Individual CLaN factor scores will be used alongside PA questionnaire results where appropriate, in regression analysis of fMRI to determine the impact of individual differences in synaesthesia phenomenology.

3.3.4 Functional Imaging

3.3.4.1 Data acquisition

Data were acquired at the Brighton and Sussex Medical School, Sussex Clinical Imaging Sciences Centre using a Siemens Avanto 1.5T system. A T1 weighted structural image was acquired (TR 1160 ms, TE 4.44 ms, flip angle 15°, voxel size 0.9 x 0.9 x 0.9 mm, 192 slices, 0.45 mm slice gap) followed by an echo-planar imaging (EPI) sequence for functional volumes (TR 2210 ms, TE 30 ms, flip angle 90°, voxel size 3 x 3 x 3 mm, 36 slices, 0.75 mm slice gap). The initiation of visual stimuli presentation was locked to the acquisition of the 6th volume, to allow for T1 saturation effects.

3.3.4.2 Colour area localisation

Colour selective areas were individually defined in both synaesthetes and controls in order to test the hypothesis that the degree of activation in colour selective areas could be predicted by individual differences in synaesthetic phenomenology, specifically in the CLaN-L

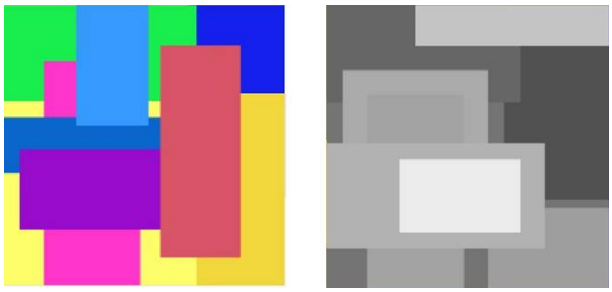


Figure 3.3: Exemplars of coloured (left) and greyscale (right) Mondrian-style stimuli used in the functional localisation of colour selective areas.

measure. Colour selective areas were functionally localised in each participant using visual presentation of alternating blocks of coloured and greyscale Mondrian-style images (see Figure 3.3), following the paradigm of Rich et al. (2006), with the addition of two extra blocks per condition. Each stimulus was presented foveally (19.5° x 19.5°) against a grey background for 1000 ms, separated by a grey isoluminant screen for 500 ms. Each block contained 14 stimuli (block duration 21 s) (see Figure 3.4). Six alternating blocks of coloured and greyscale Mondrians were presented, totalling 84 stimuli per condition and a total run duration of 252 s (see Figure 3.5). Contrasts of coloured Mondrian stimuli over greyscale Mondrian stimuli were expected to result in patterns of activation which range from bilateral ventral occipital cortex, in the area of V4, and potentially the occipital pole (V1/V2) (Mckeefry & Zeki, 1997).

The primary purpose of this contrast is to isolate 'real' colour sensitive areas in both groups in order to assess the activation related to the synaesthetic colour experience. This stimulus also provides the opportunity to assess differences between synaesthetes and controls in the processing of veridical colour. In exploratory analyses, we may see differences which account for increased colour acuity previously reported in GCS (Banissy, Walsh, & Ward, 2009). We also assess the impact of individual differences in synaesthesia phenomenology on activations related to veridical colour processing through regression of activation data against the measures described in Section 3.3.3. Regression analysis was applied to both whole brain and colour area ROI data.

3.3.4.3 Synaesthesia conditions

Inducing and non-inducing synaesthesia stimuli were used to investigate the group level synaesthetic response, specifically the differences between synaesthetes and controls, and demonstrate that the group level activations of our cohort are consistent with those reported elsewhere. Activation within the above defined colour-selective ROIs will then

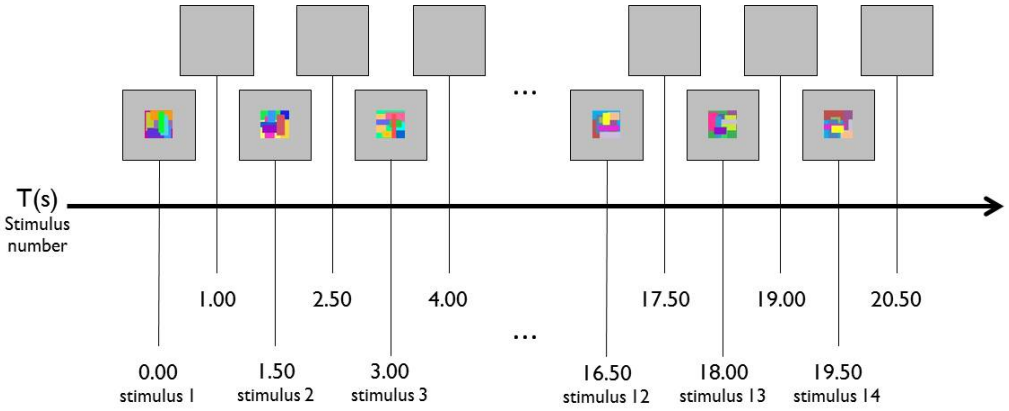


Figure 3.4: Single block of the coloured Mondrian condition of the colour area localiser stimulus. Stimuli of coloured or greyscale Mondrian-like images were presented for 1000 ms against a grey isoluminant background, separated by a 500 ms grey isoluminant screen. 14 stimuli were presented in a block (2 repeats each of 7 stimuli, in a randomised order), with a total block duration of 21 s.

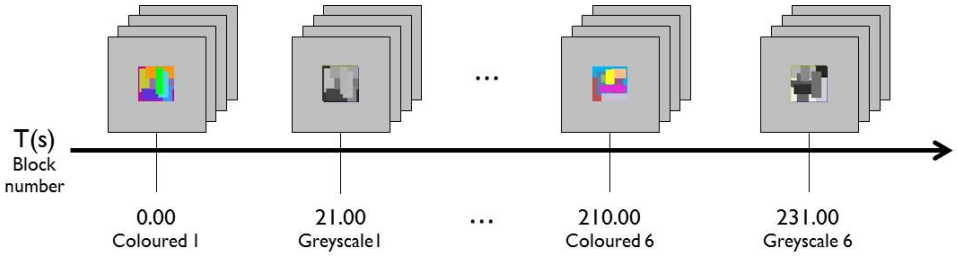


Figure 3.5: Complete run of the colour area localiser stimulus. Six alternating blocks of coloured and greyscale stimuli were presented in run, with 84 stimuli per condition and a total run duration of 252 s.

be investigated through regression analysis against CLaN-L, to test our hypothesis that CLaN-L will significantly predict colour area activity under synaesthetic conditions.

Experimental stimuli for the investigation of synaesthetic effects included two conditions, defined as below (see also Figure 3.6):

1. Inducing letters - black (lb)

2. Non-inducing symbols - black (sb)

Inducing letters were defined using the results of the Eagleman battery, as described in Section 3.3.2. Symbols consisted of commonly used punctuation (e.g. &, %, #) for which synaesthetes reported no synaesthetic experience. Stimuli were presented foveally (2-6° of viewing angle) against a grey isoluminant background.

Conditions were presented in a block design with stimuli drawn randomly from the condition set of six black letters or symbols. In each block, stimuli were presented for 2000 ms, separated with a 50 ms grey screen, with a total of 12 trials per block (block duration 24.6 s) (see Figure 3.7). Within a single run, five blocks of each condition were presented in a pseudo random order, giving a total of 60 trials per condition per run (total run duration 615 s) (see Figure 3.8). Four runs were completed per subject, giving a total of 240 trials per condition per subject. Stimuli sets and condition order for control subjects were the same as those used for their matched synaesthete. Participants were instructed to silently name the inducing letter (i.e. use inner speech) for each presented item. Based on the above conditions, it hypothesised that contrasting activation from blocks of black inducing letters (lb) against blocks of black non-induction symbols (sb) would identify areas of the brain with a role processing the synaesthetic colour concurrent over and above processing of a grapheme experience. Previous investigations have consistently reported occipito-temporal, posterior parietal, frontal and precentral region activations in group comparisons of similar contrasts.

We aim to address the conflicting evidence in activation of 'real' colour areas in the black inducers condition through independent subject-specific localisation of colour selective areas and regression of activation in those areas under synaesthetic conditions against individual CLaN-L scores. We will also conduct exploratory whole-brain regression analysis under synaesthetic conditions against CLaN-L and CLaN-A.

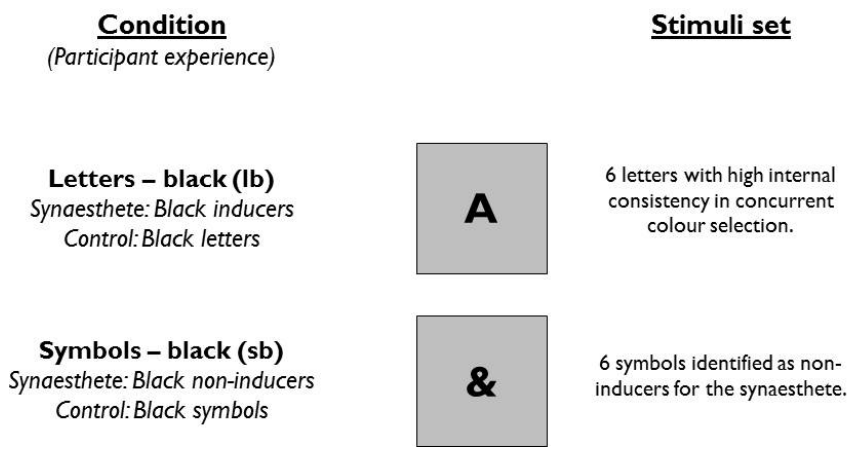


Figure 3.6: Exemplars of each condition of the experimental stimulus. Condition stimuli sets were built individually for each synaesthete tested and that same set was used for their matched control. Individual results of the online Eagleman battery (Eagleman et al., 2007) were used to identify inducing letters. Letters chosen were those with the highest consistency in concurrent colour selection (see Section 3.3.2) and to provide a variety of colours which were also easily identifiable against the grey isoluminant background.

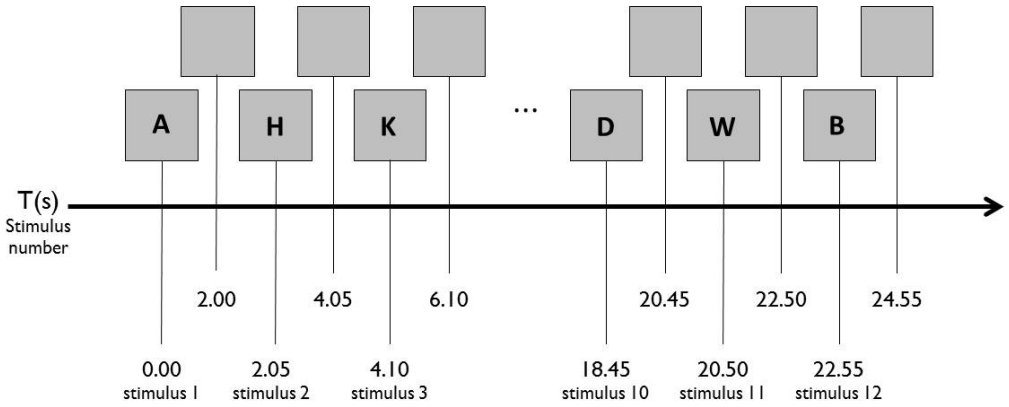


Figure 3.7: An experimental block with black inducing letters. Individual stimuli are randomly drawn from a single condition set. Stimuli were presented for 2000 ms, separated by a grey isoluminant screen for 50 ms. 12 trials were presented per block, giving a total block duration of 24.6 s.

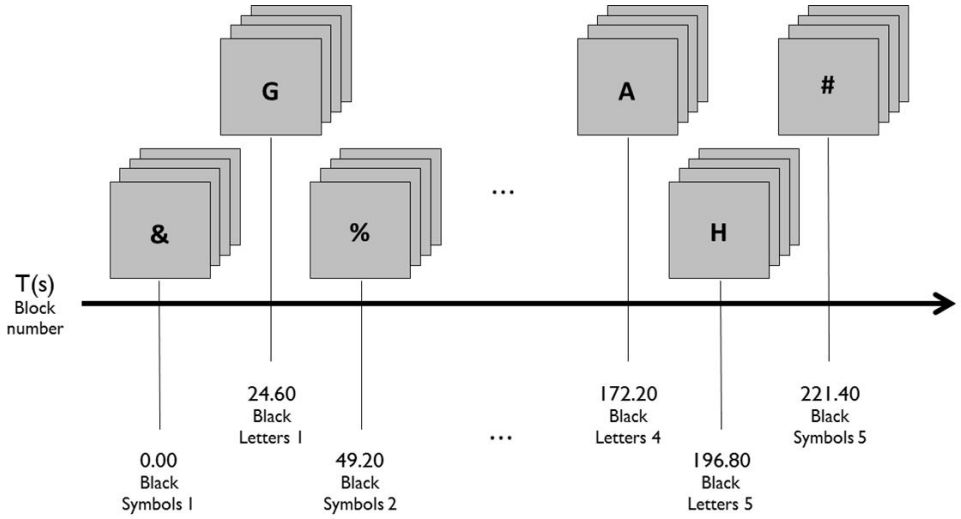


Figure 3.8: An experimental run with coloured and black inducing letters and non-inducing symbols. Five blocks of each condition were presented in a pseudo randomised order, giving a total of 60 trials per condition per run and total run duration of 615 s. Four runs were completed per subject, giving a total of 240 trials per condition per subject.

3.3.5 Image analysis

3.3.6 Preprocessing

MRI data were preprocessed and analysed with SPM8 (Wellcome Trust Centre for Neuroimaging, 2009). Preprocessing consisted of slice timing correction followed by motion correction through realignment of all EPI images using a six parameter rigid body transformation to a mean EPI image. The mean image was then co-registered with the structural and both normalised to the SPM8 MNI T1 template. The mean image normalisation parameters were then applied to the remaining EPI images. Finally, images were smoothed with an 8 x 8 x 8 mm FWHM Gaussian kernel and bandpass filtered with a 128 Hz cut-off to remove low frequency signal drifts.

3.3.6.1 General linear model

Statistical analyses were performed on the basis of the general linear model (GLM) framework. Stimulus blocks were modelled as a boxcar function convolved with the canonical haemodynamic response function (HRF) and a high-pass filter (128 s cut-off) to remove low-frequency effects. Models were estimated at the first level with the restricted maximum likelihood (ReML) approach to provide parameter estimates for each condition and enable generation of relevant contrast images. The image realignment parameters were

included as regressors of no interest in each first level model to account for variance associated with participant motions. First level contrast images were then estimated in second level random effects and two-sample group designs to enable group inferences.

3.3.6.2 ROI analysis

ROI analyses in fMRI assesses stimuli effect sizes in limited, predefined areas, thus providing significantly increased power over whole-brain analysis by reducing the number of statistical tests applied. In assessing the significance of activation in the ROI compared to the whole brain, the FWE corrected alpha is considerably larger. Because of the larger alpha and therefore higher probability of false positives in an ROI analysis compared to whole-brain analysis, it is necessary to hold strong hypotheses regarding the role and implications of findings in the assessed area. For example, in the present investigation it was hypothesised that the presentation of black inducing letters would be associated with activation in colour selective areas of the brain in synaesthetes, but that this effect may be too small to detect in whole brain analysis, as suggested by (Rouw, 2011). We therefore defined colour selective areas in our participants, using the independent colour area localiser, and assessed activation in these areas at the ROI level in the contrast of black inducing letters > black non-inducing symbols.

Individual ROIs were functionally defined in order to account for variability in topographic organisation of colour selective areas. First, an inclusive mask was built from the second level results of the colour area localiser contrast of coloured Mondrians > greyscale Mondrians (cMond > gMond), collapsed across groups[3] with an uncorrected threshold of $p < .005$ and an extent of $k = 10$. This mask was applied to each first level contrast of cMond > gMond at a reduced uncorrected threshold of $p < .05, k = 10$ (this low threshold was necessary in the first level data for the identification of BOLD response in all participants). For each subject, the global maximum response within the masked area was identified separately in the left and right hemispheres using additional left and right cerebrum inclusive masks built from the Talairach Atlas to create ROIs for a left colour selective area and a right coloured selective area. There was no significant activation at the low threshold of $p < .05$ (uncorrected) for participant 10887 (control) in the first level contrast of cMond>gMond, therefore no colour selective ROIs were identified for this subject and they were excluded from all colour area ROI analyses. For most subjects the left/right colour selective response was found to be largely symmetrical. There was no

[3]No significant differences were found at the whole brain level between groups in the contrast cMond > gMond. See Section 3.4.2.1

activation at the $p < .05$ threshold in the right hemisphere of participants 10418 (control) and 887 (synaesthete), therefore right hemisphere ROIs were generated with anatomical sagittal symmetry to the left (i.e. with positive x co-ordinate).

3.3.6.3 Covariate regression

It was hypothesised that individual differences in synaesthetic phenomenology would lead to sufficient variance in standard second level (random effects) analysis as to significantly reduce statistical power. In order to account for this first level variance, exploratory whole-brain regression analysis was performed on fMRI data using the phenomenological measures described in Section 3.3.3. This involves modelling the second level design matrix with an additional regressor of the phenomenological co-variate. Weighting the second level design to the regressor then highlights any activation which varies proportionally with the regressor in the direction specified, i.e. as a positive or negative relationship. This enables the identification of areas of activation which are significantly predicted by experiential/phenomenological aspects.

3.4 Results

To test the hypothesis that individual differences in synaesthetic phenomenology (localisation) predicts colour area activation, we conducted independent localisation of colour selective areas in synaesthetes and controls, and conducted regression analysis of the activation in these areas under synaesthetic conditions against individual CLAN-L scores. We first conducted a between group whole-brain analysis of activation under synaesthetic condition to determine whether the response of our cohort was similar to that reported elsewhere. We also conducted exploratory whole-brain analyses of the impact of individual differences in CLaN-L and CLaN-A on veridical colour processing, to determine the wider reaching impact of these aspects of the synaesthetic experience.

3.4.1 Synaesthesia phenomenology

3.4.1.1 Colour Letters and Numbers questionnaire

The CLaN questionnaire can be subdivided into four factors relating to specific aspects of the subjective synaesthetic experience. Of particular relevance here are the factors which relate to the automaticity of the synaesthetic concurrent experience and the spatial localisation of the concurrent, as described below.

Automaticity (CLaN-A) High scores denote an automatic experience of the concurrent, without the need for specifically directed attention to the synaesthetic experience, i.e. the participant reports awareness of concurrents without directed attention towards the concurrent experience, for example they are normally aware of their synaesthetic colours whilst reading, without intentionally focussing in the synaesthetic experience.

Localisation (CLaN-L) High scores are obtained if the participant reports an externalised concurrent experience, such that they can point to where the concurrent exists in an area of space.

Distributions of scores for CLaN-L ($mean = 13.32, sd = 5.02$) and CLaN-A ($mean = 14.05, sd = 4.38$) are shown in Figure 3.9. In both measures, the distribution was not significantly different from normal and therefore suitable for parametric analysis (For CLaN-L Kolmogorov-Smirnov (KS) $D(20) = 0.177, p = .100, zskew = 0.588, zkurtosis = -1.163$; CLaN-A: (KS) $D(20) = 0.113, p = .200; zskew = -1.049$, $zkurtosis = -1.184$).

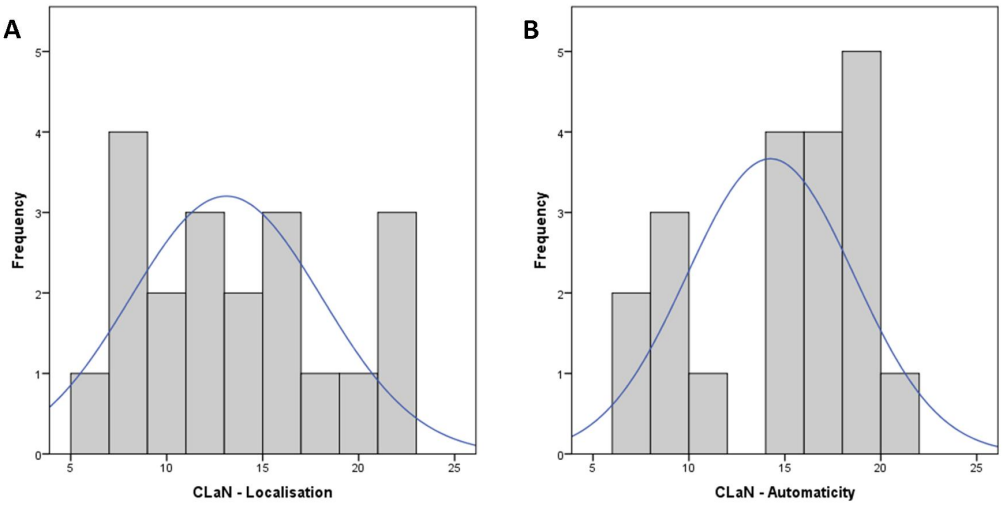


Figure 3.9: Frequency distributions of scores on CLaN questionnaire (Rothen, Tsakanikos, et al., 2013) (A) CLaN-L ($mean = 13.32, sd = 5.02; (KS)D(20) = 0.177, p = .100, zskew = 0.588, zkurtosis = -1.163$) and (B) CLaN-A ($mean = 14.05, sd = 4.38; (KS)D(20) = 0.113, p = .200; zskew = -1.049,\ zkurtosis = -1.184$). Distributions of scores on the CLaN measures are not significantly different from a Normal, continuous distribution.

3.4.1.2 Projector-Associator measures

In order to describe our cohort in terms consistent with the existing literature, synaesthetic participants completed both the Illustrated Synaesthesia Experience Questionnaire (ISEQ) (Skelton et al., 2009) and the Rouw and Scholte Projector-Associator (RS-PA) (Rouw & Scholte, 2007). Exploratory analysis was conducted on the relationship between these existing measures and the CLaN-L score, to determine whether these different measures were independent.

The results of the ISEQ and RS-PA questionnaires were positively correlated (Pearson's correlation coefficient R = .846, $p < .001$), suggesting that there is significant agreement between the measures in terms of PA phenomenology in our sample. Both questionnaires classified 2/20 participants (px821 and px887) as projectors, however the ISEQ classified 2/20 participants (px418 and px472) as "undetermined" as they rated both projector-type and associator-type questions equally (see Figure 3.10).

The CLaN factor of localisation (CLaN-L) is similar in kind to the PA dimension of ISEQ and RS-PA, and accordingly had a significant positive relationship with both measures (RS-PA Pearson's R = .626, $p = .002$; ISEQ Pearson's R = .525, $p = .011$). In CLaN-L however, three participants scored equal to or higher than those identified as

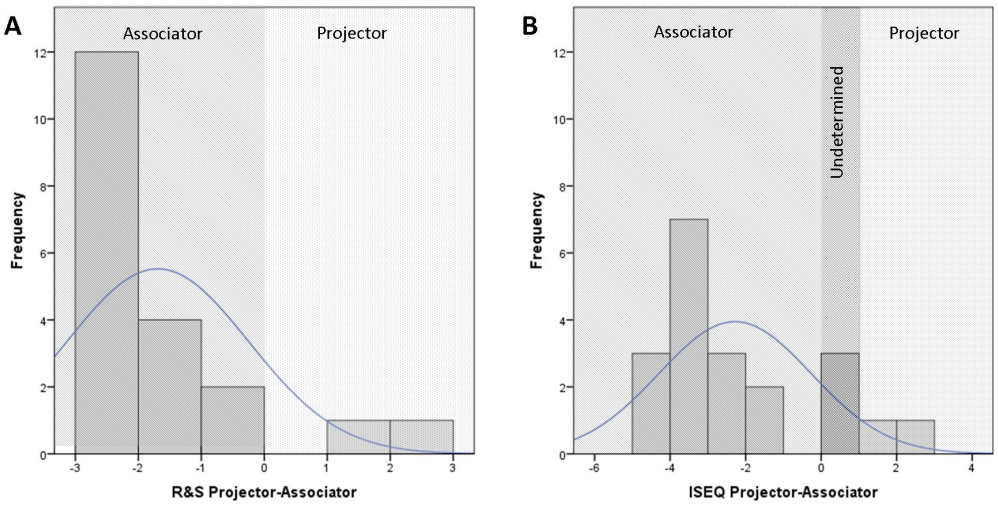


Figure 3.10: Frequency distributions of scores on (A) RS-PA (Rouw & Scholte, 2007) and (B) ISEQ (Skelton et al., 2009) with categorical distinctions in projector-associator subgroupings where relevant. The data illustrate the approximately bimodal distribution in scores across both projector-associator measures as the questionnaires are designed for dichotomous labelling of the phenomenological experience.

projectors in the ISEQ and RS-PA measures (px355, px400, px584), suggesting that the CLaN-L and ISEQ/RS-PA measures do not measure exactly the same phenomenological experience. This suggests that although there is general agreement between these three measures, as demonstrated by the significant positive relationship, there is some ambiguity at the subject level regarding the appropriate categorical classification of phenomenology on a projector-assocaitor dimension.

The RS-PA measure showed significant skew ($zskew = 3.55$) which was not reduced by log transformation. This questionnaire was developed to identify members of two distinct categories, rather than produce a continuous measure, therefore any attempt to reduce the skew by the exclusion of our two 'projector' participants would reduce our sample to a single dimension.

3.4.1.3 Eagleman battery

The Eagleman battery was used to qualify GCS in the synaesthetic participants only and also identify concurrent colours for the purposes of stimulus generation. In qualifying participants, Eagleman et al. (2007) suggest a threshold of 1 in consistency scores for the correct identification of synaesthetes. The mean consistency in our participants was 0.80 (sd = 0.26), suggesting that as a group they do meet the threshold criteria set by Eagleman

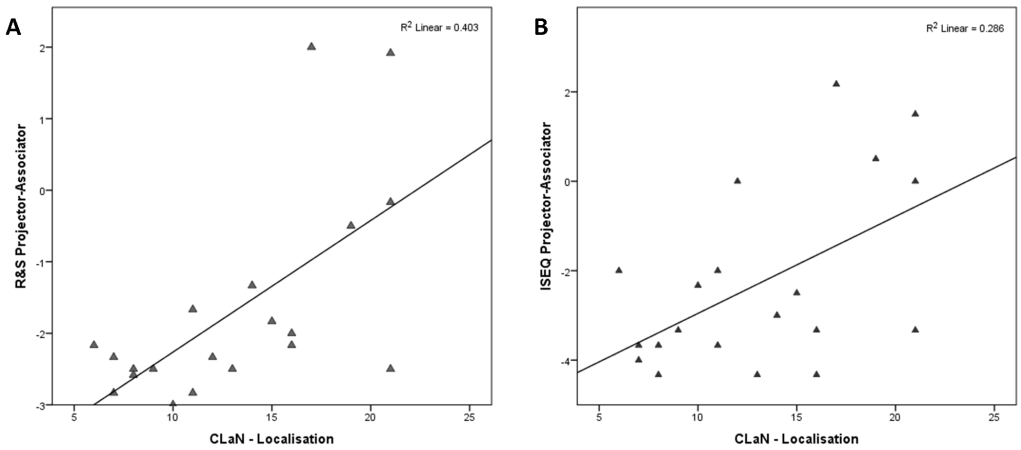


Figure 3.11: Correlation between PA measures across three assessed questionnaires. Both measures were positively correlated with CLaN-L: (A) RS-PA ($R = .626, p = .002$); and (B) ISEQ ($R = .525, p = .011$).

et al. (2007) and show sufficient consistency in their colour selections to suggest that the associations are specific and automatic. Six of our participants exceeded the consistency threshold of 1 suggested by Eagleman et al. (2007), however, all participants met the revised consistency criteria suggested by Rothen, Tsakanikos, et al. (2013) (maximum consistency score = 1.24) and CIELUV transformed consistency threshold of 135 ($mean = 72.11, sd = 28.30$). In the speeded congruency test, synaesthetes scored a mean of 87.6% correct ($sd = 5.55\%$) and mean reaction time of 1.65 s ($sd = 0.54s$). These results demonstrate that our participants had reduced accuracy and increased reaction times compared to the sample population used in Eagleman et al. (2007) (mean accuracy = $94\%, rt = 0.64s \pm 0.78s$).

3.4.2 Functional imaging

3.4.2.1 Colour area localisation

To confirm that the effects of the localiser stimuli are in agreement with other published investigations, data from the Mondrian stimuli were collapsed across the groups to identify those areas which are reliably activated in both populations (Figure 3.12 and Table 3.1). This pooled random effects analysis identified the maximal response and significant FWE corrected peak in the left fusiform gyrus at -26 -68 -16 ($Z = 5.52, p(FWEpeak) = .002$), close to previously reported co-ordinates for V4. Further significant peaks were also identified in the left calcarine sulcus at -12, -98, -2 ($Z = 5.51, p(FWEpeak) = .002$) and the left fusiform gyrus at -26, -78, -12 ($Z = 5.40, p(FWEpeak) = .004$). These findings are in

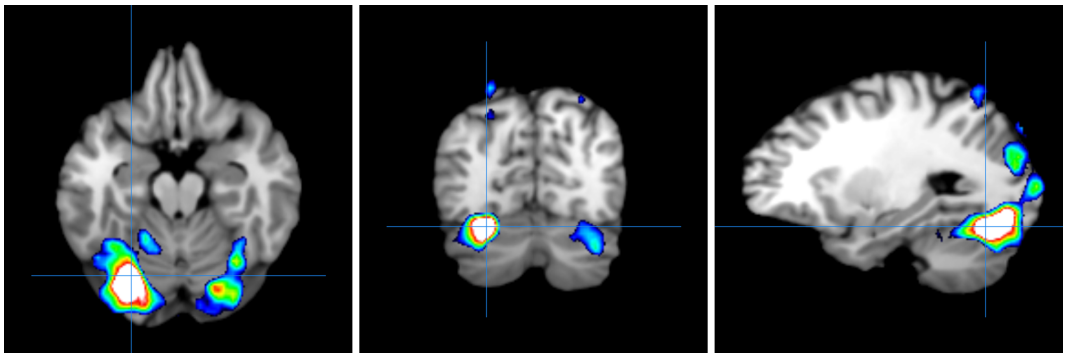


Figure 3.12: Pooled random effects analysis of synaesthetes and controls in the contrast of cMond > gMond. Cross-hairs positioned at the global maximum peak at -26, -68, -16 ($Z = 5.52, p(FWEpeak) = .002$. Activation pattern suggests successful localisation of colour selective areas in these subjects, with the global maximum peak close to reported V4 co-ordinates. Colour scale represents t-score range from 2.71 to 5, equivalent to uncorrected height threshold $p < .005$ to $p<.001$

agreement with previous investigations of colour selective areas, particularly related to V4 activation, and suggest that we have successfully localised the colour selective response in these participants. Analysis of the Mondrian (cMond > gMond) contrasts identified no significant FWE corrected differences between groups at the whole-brain level, i.e. there were no large scale group differences between synaesthetes and controls in the response to physical colour in Mondrian stimuli.

Colour area ROIs were generated separately in the left and right hemisphere for each synaesthete and control, based on the maximally activated area in first level activation maps of coloured Mondrian > greyscale Mondrians, masked by the second level data of the same contrast, collapsed across both groups. The distribution of colour areas was found to be largely similar between synaesthetes and controls, as shown in Figure 3.13 and Figure 3.14.

3.4.2.2 Synaesthetic colour processing

The primary focus of synaesthesia imaging research has thus far related to the neurological activity involved in the experience of black inducing letters and the accompanying experience of synaesthetic colour. GLM analysis of black inducing letters against the control condition of black non-inducing symbols (lb>sb), was predicted to highlight the areas relevant to processing the synaesthetic colour experience over and above a black grapheme-like experience, in areas which have been consistently reported across different cohorts.

Table 3.1: Significant clusters and peaks in whole-brain analysis of coloured Mondrians > greyscale Mondrians. Areas identified as from the combined data of all 40 subjects. No significant FWE corrected whole-brain differences were identified between the groups, therefore separate data for each group is not presented. Area names as identified with the AAL toolbox for SPM (Tzourio-Mazoyer et al., 2002).

Area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
		Collapsed across groups					
Fusiform gyrus (L)	<.001	6119	.002	5.525	-26	-68	-16
Calcarine sulculs (L)			.002	5.509	-12	-98	-2
Fusiform gyrus (L)			.004	5.398	-26	-78	-12

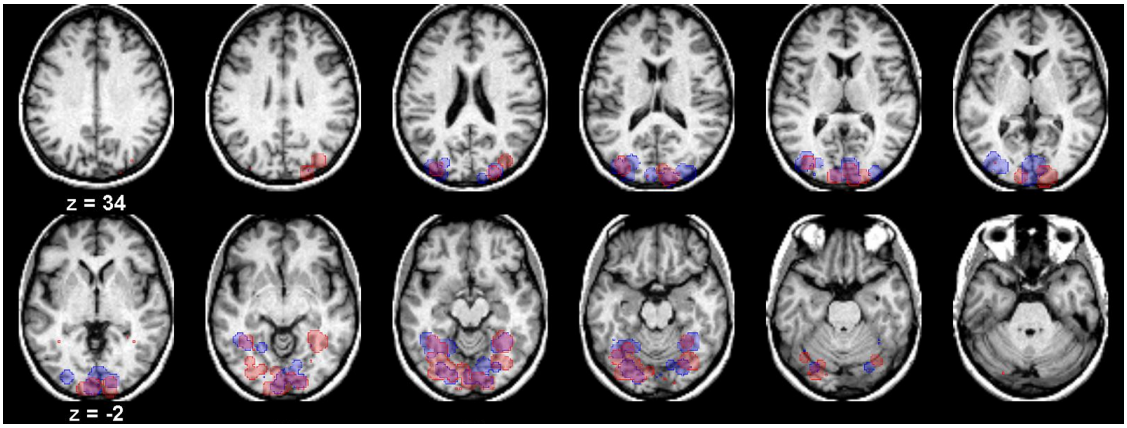


Figure 3.13: Participant colour selective ROIs generated for synaesthetes (red) and controls (blue), demonstrating a largely similar distribution of maximally responsive areas to veridical colour in both groups. ROI size 8 mm radius.

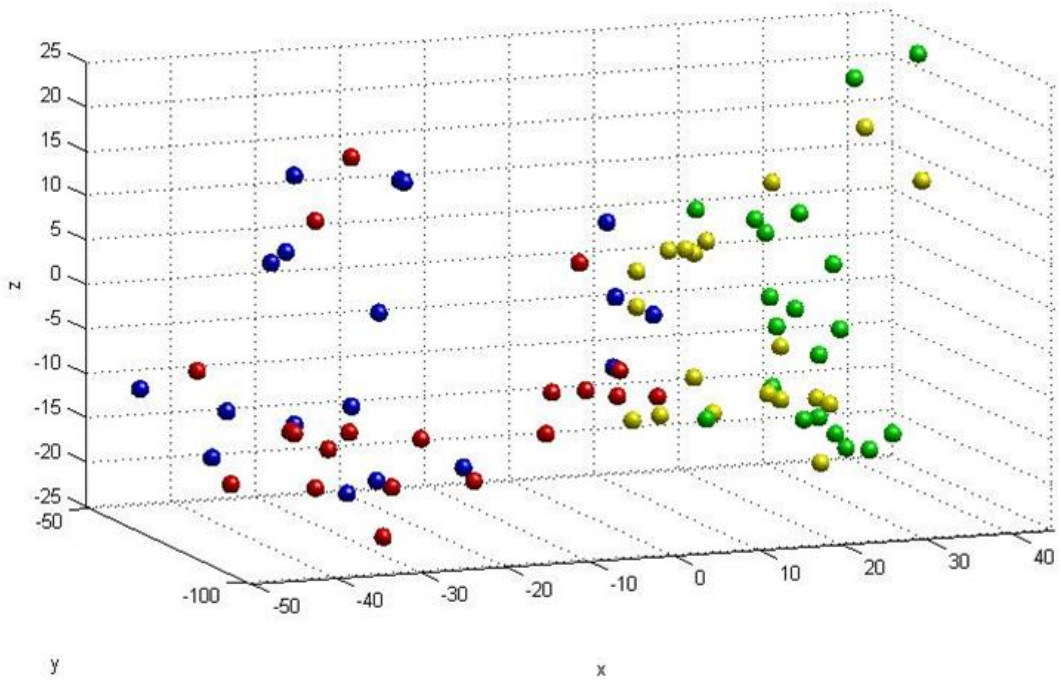


Figure 3.14: Positioning of participant colour-selective ROIs in 3D MNI space. Red = synaesthetes left colour area; green = synaesthetes right colour area; blue = controls left colour area; yellow = controls right colour area. All ROIs are within the occipital lobe, V1-V5. The distributions demonstrate a similar localisation of maximally responsive areas in synaesthetes and controls. See also Appendix B.4.

Such whole-brain analyses regularly reveal activation in occipito-temporal, posterior parietal, frontal, precentral and insula regions when comparing effects in synaesthetes verses controls (Rouw et al., 2011). Less consistent, however, are reports of activation in real colour areas in response to black inducers, in whole-brain or ROI analysis. We hypothesised that the conflicting results may be an effect of individual differences in synaesthesia phenomenology, and specifically that the degree of activation in colour selective areas could be predicted by individual differences in CLaN-L scores.

In the present data, we observe a group by synaesthetic induction interaction in the contrast of lb>sb, with significant FWE corrected clusters of activation in the left precentral gyrus and bilateral inferior parietal gyrus (see Figure 3.15 and Table 3.2). The pattern of activation is consistent with those areas identified by the Rouw et al. (2011) review as being highly reproducible across different investigations of GCS. If both corrected and FWE uncorrected significant peaks are included, as they are in the mappings of the Rouw et al. (2011), there is a strong replication of the occipito-temporal, posterior parietal, precentral and dorsolateral prefrontal clusters of activation identified across different imaging studies using the same condition and group contrasts. Figure 3.16 is provided for comparison with the results of the Rouw et al. (2011) meta-analysis, demonstrating that our activation falls within the range of areas previously identified as relevant to synaesthesia[4]. In the posterior parietal areas, the response in our participants is slightly more anterior and superior than those reported in Rouw et al. (2011), however Rouw et al. (2011) note a general variation in the localisation of posterior parietal activation across studies. We also note that the areas identified in the present study are minimally significant at the $p < .005$ threshold, whereas those studies included by Rouw et al. (2011) reported uncorrected thresholds from $p < .05$, suggesting that the whole-brain results here are of similar or increased power compared to data obtained from other sample populations. These data are strongly suggestive of the induction of a synaesthetic state in our subjects which is qualitatively and quantitatively similar to synaesthesia investigations conducted elsewhere, despite differences in methodology (our stimuli were passively viewed where others have included an active task with attentional monitoring) and the relative distribution of our subjects across the projector-associator scale.

In addressing the question of colour area activation at the group level, we find no significant peaks or clusters in the region of V4 when assessing whole-brain group differences.

[4]ROIs in 3.16 are 13 mm radius spheres positioned on the co-ordinates given in slice positioning of Rouw et al. (2011) Figure 1A-D. Where no co-ordinates were supplied, the centre of the ROI was interpolated from the central peak activation

Table 3.2: FWE corrected significant clusters in the contrast of lb>sb in synaesthetes > controls.

Area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
			Synaesthetes > Controls				
Precentral (L)	.023	437	.603	4.051	-46	4	34
Inferior parietal (L)	.001	750	.604	4.050	-46	-48	50
Inferior parietal (R)	.014	480	.902	3.765	44	-48	48

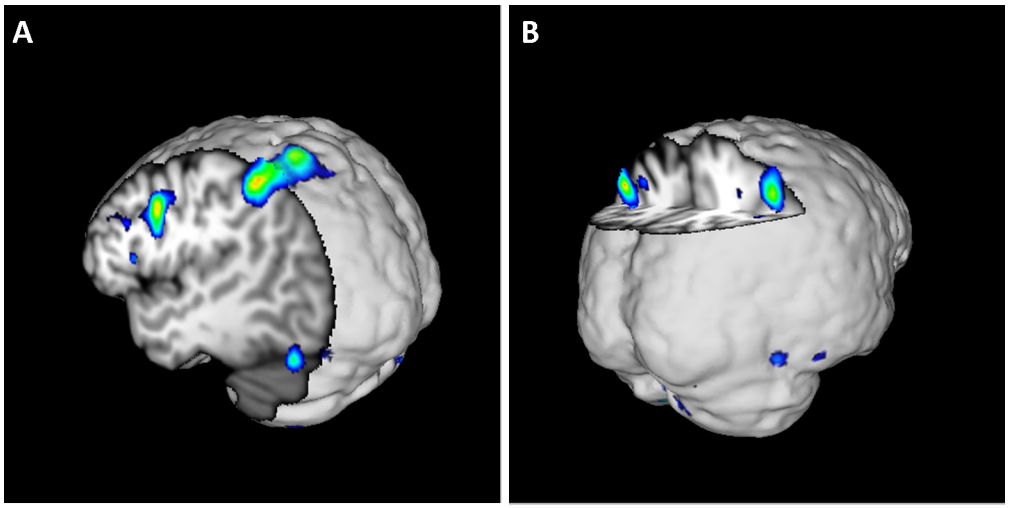


Figure 3.15: Whole-brain analysis in synaesthetes > controls of the contrast black letters > black symbols. Colour scale represents t-score range from 2.71 to 5, equivalent to uncorrected height threshold $p < .005$ to $p < .001$. Cut planes positioned to show significant FWE corrected clusters in A) left precentral [-46, 4, 34]($k = 437, p(FWEcluster) = .023, Z = 4.051, p(FWEpeak) = .603$) and left inferior parietal cortex [-46, -48, 50]($k = 750, p(FWEcluster) = .001, Z = 4.050, p(FWEpeak) = .604$); B) left and right inferior parietal cortex [44, -48, 48]($k = 480, p(FWEcluster) = .014, Z = 3.765$ $p(FWEpeak) = .902$)

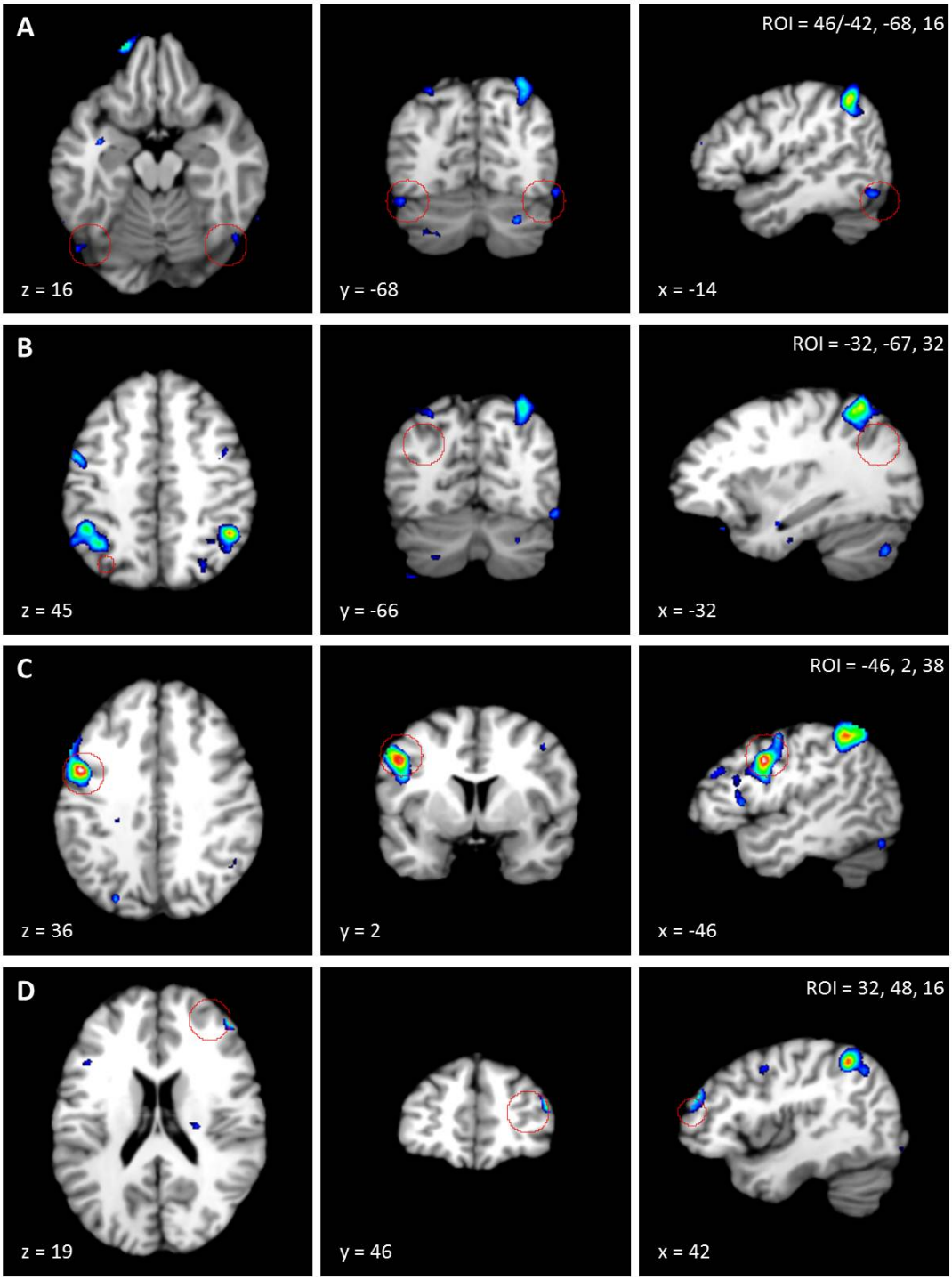


Figure 3.16: Whole-brain analysis in synaesthetes > controls of the contrast lb>sb, demonstrating the correspondence between activation identified in the present study and that shown to be consistent across investigations (Rouw et al., 2011). Clusters of activation are found in four areas (circled red): A) occipito-temporal cortex; B) posterior parietal cortex; C) precentral cortex; D) dorsolateral prefrontal cortex. Colour scale represents t-score range from 2.71 to 5, equivalent to uncorrected height threshold $p < .005$ to $p < .001$.

These occipito-temporal peaks are too distant from V4 to be considered 'real colour area' activation in response to synaesthetic colour and also of insufficient power to be reliably distinguished from noise on a post hoc basis. This suggests that at the group level, there is no colour area activation in response to synaesthetic colour. This is in accordance with the majority of the existing literature in which colour area activation was not successfully replicated, and in line with our hypothesis that the low proportion of projectors in our cohort ($n = 2$) will preclude the observation of a group level colour area response in whole-brain analyses.

Given the low sensitivity of whole-brain analysis and variability in topographical colour area activation, we have also applied the subject-specific colour selective ROI analysis to the contrast of lb>sb (see Figure 3.17). In both synaesthetes and controls, these areas show a non-significant response to synaesthetic colour in both left (synaesthetes mean $\beta = 0.151, t = 1.183, p = .126$; controls mean $\beta = -0.169, t = -1.521, p = .928$) and right hemisphere colour selective ROIs (synaesthetes mean $\beta = 0.005, t = 0.019, p = .492$; controls mean $\beta = -0.284, t = -2.224, p = .981$). These findings suggest that the areas defined as 'colour selective' are not significantly responsive in synaesthetic colour conditions in synaesthetes or controls and there is no significant activation in letter processing areas associated with this contrast. This is again in line with our hypothesis that the low proportion of projectors in our cohort ($n = 2$) will preclude the observation of a group level colour area response, even in sensitive ROI analyses.

Activations within colour processing areas were assessed for normality in order to identify group level differences by parametric testing (see Table 3.3). There were significant deviations from normality in data, including significant positive skew in 1/4 ROIs, significant negative skew in 2/4 ROIs and positive kurtosis in 2/4 ROIs (see Table 3.3). Given both the positive and negative skew in these data, it is unlikely that these issues will be resolved by a single transformation. We note, however, that all data appeared within the range of a normal distribution as demonstrated by the KS test. Further analysis was therefore conducted on the untransformed data and supported by further non-parametric assessment where necessary.

A mixed ANOVA was conducted with the between subjects factor 'group' (synaesthetes and controls) and the within subjects factor 'ROI' (colour area left and colour area right). Analysis showed no significant main effect of ROI ($F(1, 38) = .870, p = .357$) demonstrating that results obtained from each ROI are not significantly different from each other. There was no significant main effect of group ($F(1, 38) = 3.047, p = .089$), and synaes-

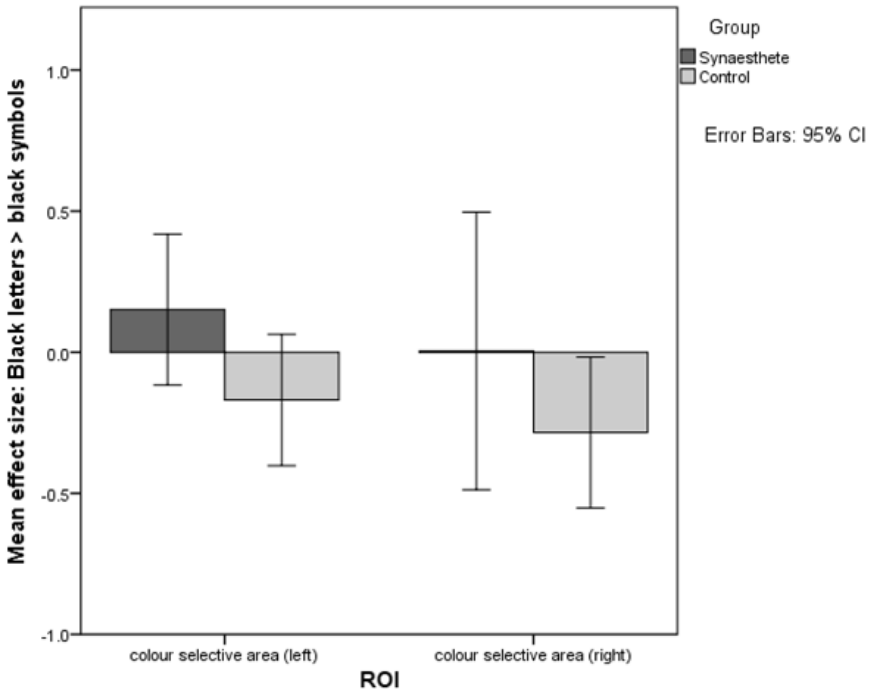


Figure 3.17: ROI results from colour area experimental contrast of black letters > black symbols. Effect sizes are SPM betas - a standardised effect size across conditions. No evidence is found to suggest colour areas activation in synaesthetes in response to synaesthetic colour. Control colour selective area left $t(19)$ = -1.521, p =.928; control colour selective area right $t(19) = -2.224, p = .981$; synaesthete colour selective area left $t(19) = 1.183, p = .126$; synaesthete colour selective area right $t(19) = 0.019, p = .492$. Between groups colour selective area left $F(1, 38) = 1.175, p = .285$; colour selective area right $F(1, 38) = 0.428, p = .517$.

Table 3.3: Assessment of normality in ROI data on the contrast of lb>sb in untransformed data. ∗significant at $p < .05$, ∗∗significant at $p < .01$, ∗∗∗significant at $p < .001$.

ROI	Group	zskew	zkurt	KS statistic	*p*(KS)	Levene's statistic	p(Levene's) Median
			Untransformed data				
Left colour areas	Control	3.046**	4.921***	0.169	.135	0.772	.385
	Synaesthete	-0.664	-0.390	0.109	.200		
Right colour areas	Control	-2.050*	1.631	0.179	.093	3.016	.091
	Synaesthete	-3.733***	5.702***	0.186	.069		

thetes ($M = 0.078, 95\%CI = -0.172 - 0.328$) showed slightly increased mean activation across all ROIs together compared to controls ($M = -0.227, 95\%CI = -0.477 - 0.023$). There was no significant ROI-by-group interaction ($F(1, 38) = 0.013, p = .912$), indicating that there was no significant difference between activation in the ROIs dependant on group membership. Planned comparisons demonstrated a significant difference between groups in left colour area activation ($t(38) = -1.892, p = .033$), with synaesthetes having a higher mean response ($M = 0.151$) than controls ($M = -0.178$). There was no significant difference between groups in right colour area activation ($t(38) = -1.079, p = .144$). These data demonstrate that overall, there is no significant difference in the response to synaesthetic colour between synaesthetes and controls in those areas we previously identified as responsive to colour. There is, however, a marginal trend for an increased response in our sample of synaesthetes but data show large variation in both synaesthetes and controls.

It is possible that the inter-subject variability in the first level limits population-level inference at the second level. We hypothesised that individual differences in CLaN-L would predict the degree of colour area activation and subsequently performed whole-brain and ROIs regression analysis on the black inducers contrast (lb>sb). A significant positive relationship was found to exist between a number of areas in whole-brain analysis, as listed in Table 3.4 and Table 3.5. Participants with localised concurrents showed greatest activation in the left precentral gyrus, left insula, right cerebellar crus 1, left median cingulate gyrus and left supplementary motor area (see Figure 3.18). The cluster in the left precentral gyrus shows considerable overlap with the left precentral cluster identified in the main effect of synaesthesia, suggesting that this area is both a general effect of synaesthesia and related to the phenomenological variation of this cohort. All other whole-brain regression clusters are distinct from the main effects.

It was hypothesised that CLaN-L scores would predict the degree of activation in colour areas under synaesthetic conditions. Accordingly, regression of left and right colour area responses against CLaN-L both showed a significant positive relationship, such that the greater the degree of localisation of the synaesthetic concurrent, the greater the magnitude of activation found in left ($R = .489, p = .029$) and right ($R = .489, p = .029$) colour selective areas under synaesthetic conditions (see Figures 3.19 A-B).

In summary, we have successfully reproduced patterns of activation in the group interaction contrast of lb>sb which are quantitatively and qualitatively similar to those obtained by other synaesthesia investigations. In line with a number of these investigations, there was no evidence of colour area activation in response to synaesthetic colour

Table 3.4: FWE corrected clusters of BOLD activation identified in whole-brain regression analysis of synaesthetes in the contrast lb>sb.

Area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
Synaesthetes: CLaN-L							
Precentral (L)	<.001	743	.802	4.006	-44	2	36
Insula (L)	.038	341	.894	3.899	-34	16	10
Cerebellar Crus1 (R)	.013	421	.955	3.790	38	-70	-32
Median cingulate gyrus (L)	.042	334	.964	3.768	-20	-36	30
Supplementary motor area (L)	.006	489	.988	3.668	-8	4	62
Synaesthetes: CLaN-A							
Middle occipital (R)	.001	661	.642	4.140	40	-74	2

Table 3.5: Regression statistics from FWE corrected clusters identified in whole-brain regression analysis of synaesthetes in the contrast lb>sb.

Area	Beta	95% CI	β	t	p	R^2	R^2Adj.	$F_{(1,18)}$	p
Synaesthetes: CLaN-L									
Median cingualte (L)	.035	0.020-0.050	.758	4.925	<.001	.574	.550	24.256	<.001
Precentral (L)	.054	0.029-0.079	.728	4.509	<.001	.530	.504	20.331	<.001
Insula (L)	.035	0.018-0.053	.709	4.266	<.001	.503	.475	18.200	<.001
Cerebellar Crus1 (R)	.090	0.044-0.135	.698	4.131	.001	.487	.458	17.067	.001
Supplementary motor area (L)	.047	0.022-0.072	.684	3.978	.001	.468	.438	15.824	.001
Synaesthetes: CLaN-AA									
Middle occipital gyrus (R)	.047	0.026-0.067	.747	4.765	<.001	.558	.533	22.707	<.001

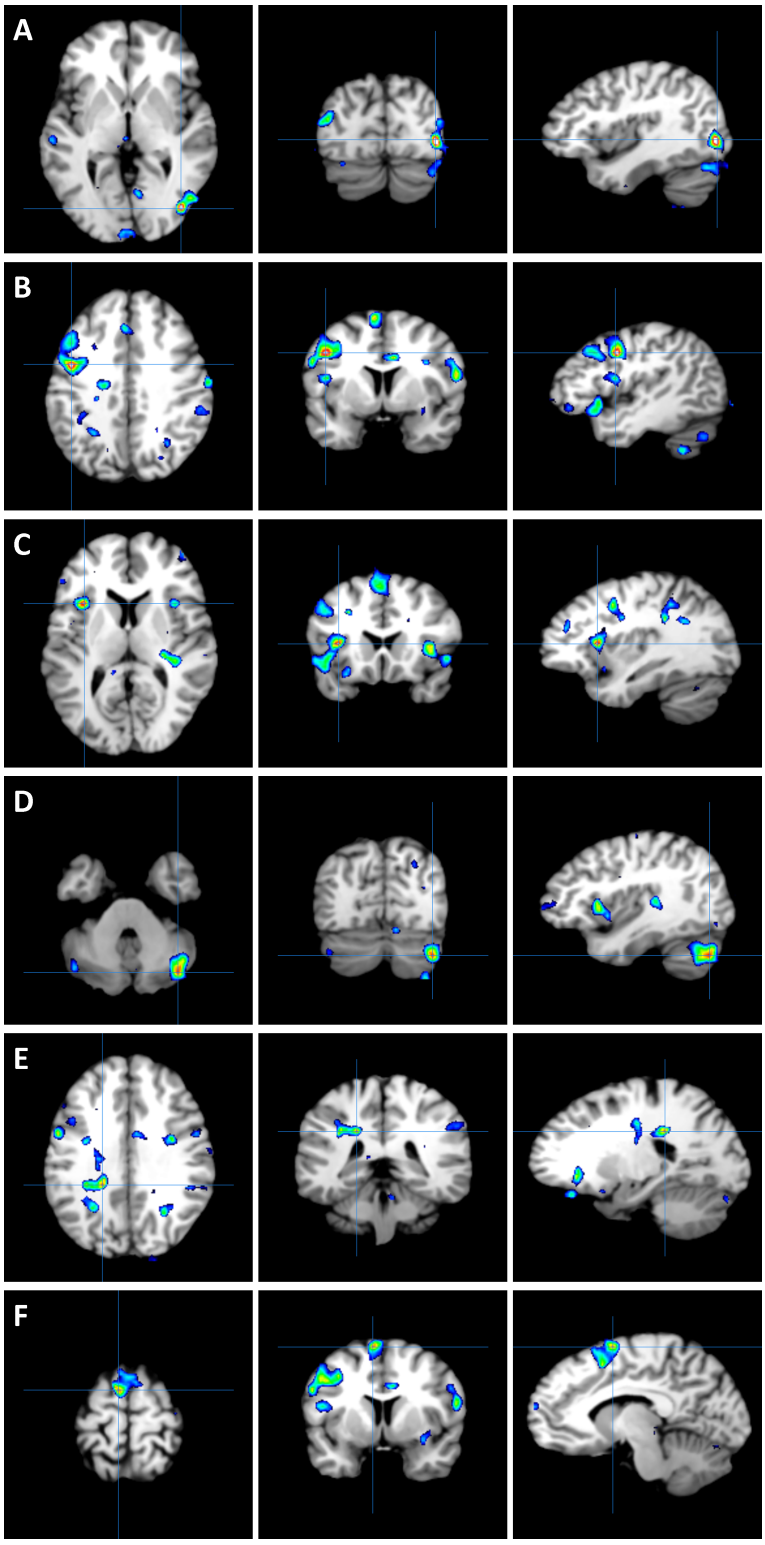


Figure 3.18: FWE corrected clusters in synaesthetes lb>sb following whole-brain regression against CLaN-A (A) and CLaN-L (B-F). A) Right middle occipital gyrus [40, -74, 2] ($k = 661, p(FWEcluster) = .001, Z = 4.140, p(FWEpeak) = .642$); B) left precentral gyrus [-44, 2, 36] ($k = 743, p(FWEcluster) < .001, Z = 4.006, p(FWEpeak) = .802$); C) left insula [-34, 16, 10]($k = 341, p(FWEcluster) = .038, Z = 3.899, p(FWEpeak) = .894$); D) right cerebellar crus I [38, -70, -32] ($k = 421, p(FWEcluster) = .013, Z = 3.790, p(FWEpeak) = .955$); E) left median cingulate gyrus [-20, -36, 30] ($k = 334, p(FWEcluster) = .042, Z = 3.768, p(FWEpeak) = .964$); F) left supplementary motor area [-8, 4, 62] ($k = 489, p(FWEcluster) = .006, Z = 3.668, p(FWEpeak) = .988$).

either in the whole-brain or the clearly defined colour selective ROIs, when the group of synaesthetes is taken as a whole. In accordance with our hypothesis, we find that there is a significant positive relationship between colour area activation and CLaN-L, such that the degree of colour area response may be predicted by individual differences in localisation of synaesthetic concurrents, with greater localisation predicting greater activation in colour selective areas.

3.4.3 Exploratory analysis: Effects of individual differences in CLaN-A on synaesthetic colour processing

The CLaN factor of automaticity (CLaN-A) is a newly defined phenomenological measure of the degree of automaticity of the synaesthetic experience reported by participants, where a high scores denotes an automatic experience of the concurrent, without the need for specifically directed attention to the synaesthetic experience. The present investigation is the first application of this measure to neural data, and thus only weak predictions were made regarding the impact of this aspect on regional activation. Specifically, we proposed that activation in frontal areas under synaesthetic conditions might correlate with CLaN-A scores, as these areas are normally implicated in attentional functions. For completeness, regression in colour selective ROIs against CLaN-A was also conducted, to determine the impact of this individual difference on colour area activity.

In whole-brain regression, only the right middle occipital gyrus was found to have a significant positive relationship with CLaN-A. In ROI analysis of colour selective areas, CLaN-A was found to significantly predict activation in the left colour selective area ($R = .461, p = .022$), but not the right colour selective area ($R = .088, p = .363$) (see Figure 3.19 C-D).

As both CLaN-L and CLaN-A were found to predict colour area activity, hierarchical regression models were constructed with the inclusion of both phenomenological variables to determine the relative influence of each on the degree of colour area response under synaesthetic conditions. The top level of these hierarchical models was assigned to CLaN-L as this measure related to our primary hypothesis and also showed significant predictive power over more whole-brain regions than CLaN-A. The results of the hierarchical regression involving both phenomenological measures are presented in Table 3.6, where model 1 includes only CLaN-L and model 2 includes both CLaN-L and CLaN-A.

As required for hierarchical regression, there was no evidence of multicollinearity in the left colour area data; bivariate correlations between ROI activation for CLaN-L and

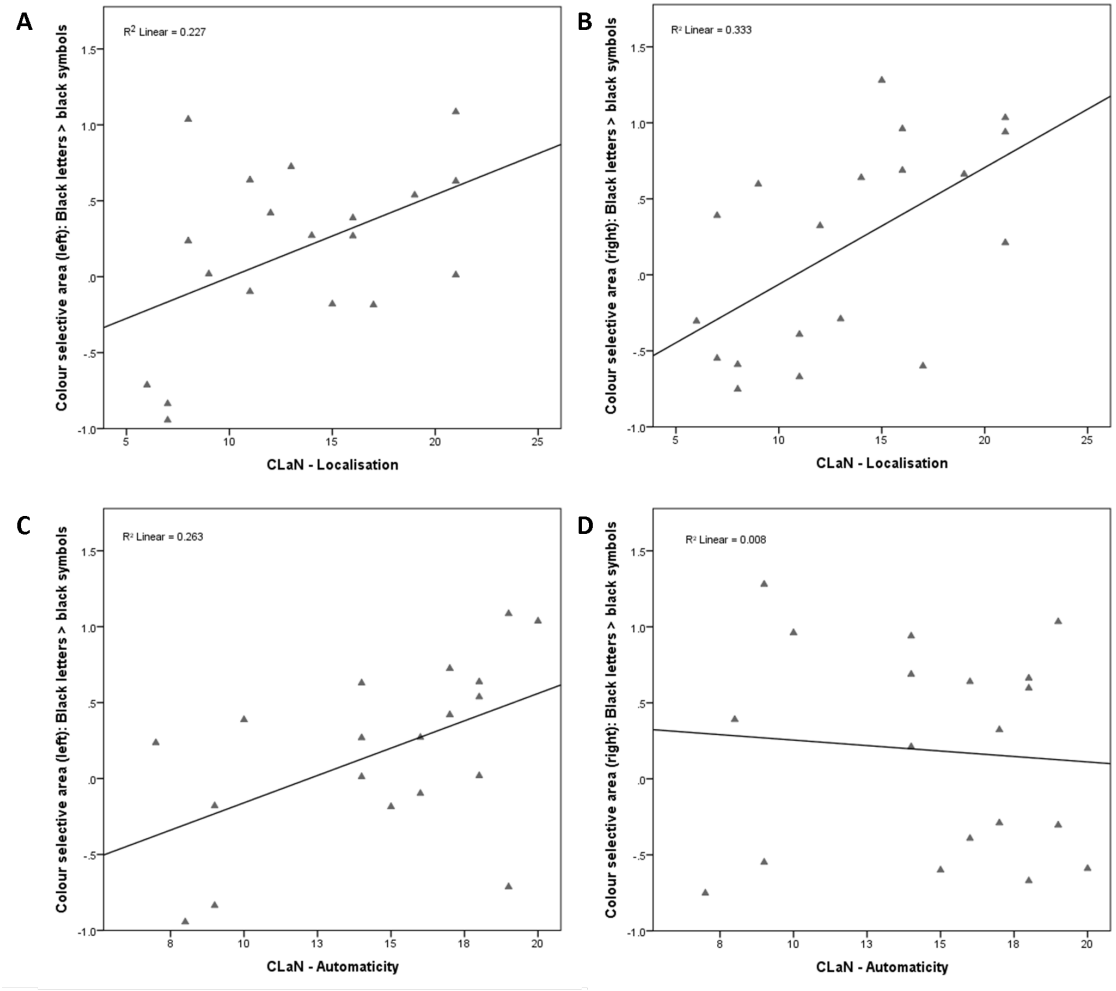


Figure 3.19: Linear regressions of ROI data against phenomenological measures. A) left colour area activation correlation against CLaN-L ($R = .489, p = .029$); B) right colour area activation correlation against CLaN-L ($R = .489, p = .029$); C) left colour area activation correlation against CLaN-A ($R = .461, p = .022$) ; D)right colour area activation correlation against CLaN-A ($R = .088, p = .363$)

Table 3.6: Regression statistics in synaesthete colour selective areas in lb>sb against two stage hierarchical model of CLaN-L (L) and CLaN-A (A).

Model	beta	95% CI	β	t	p	R^2	R^2Adj.	$F_{(1,18)}$	p(F)	p (F change)
Left colour selective area										
Model 1 (L)	0.056	0.007-0.106	.489	2.381	.029	.240	.197	5.670[1]	.029	.029
Model 2 (L)	0.047	0.002-0.091	.407	2.218	.040	.446	.380	6.833[2]	.007	.022
Model 2 (A)	0.061	0.010-0.111	.461	2.514	.022					
Right colour selective area										
Model 1 (L)	0.077	0.021-0.132	.577	2.916	.010	.333	.294	8.500[3]	.010	.010
Model 2 (L)	0.093	0.023-0.137	.439	2.059	.055	.361	.281	4.517[4]	.028	.419
Model 2 (A)	0.043	-0.097-0.043	.178	0.0835	.416					

CLaN-A were all $R < .8(range = .178 - .534)$; tolerance was $< 10(T = 0.968)$; variance inflation factor (VIF) was $> .2(VIF = 1.033)$. There was slight negative autocorrelation (Durbin-Watson $d = 2.331$) but this is within the acceptable limits of 1.52.5.

In the right hemisphere colour selective area, one participant was found to have a standardised residual of -3.009 and exerting a large influence on the regression models with a Cook's distance of .956. With a sample size of $n = 20$ we would expect only 0.2 participants to have a standardised residual > 2.58 in a normal distribution, thus although the Cook's distance is within the acceptable limit (< 1), this participant was excluded from the regression analysis. With this participant excluded, there was no evidence of multicollinearity as bivariate correlations were $< .8$ (range $-.088 - .577$), tolerance was < 10 ($T = .982$) and VIF $> .2$ ($VIF = 1.018$). There was a slight negative autocorrelation ($d = 2.472$) but this was within the acceptable range.

For the left colour selective area, the prediction of ROI BOLD is significantly better than the mean in both Model 1 ($F(1, 18) = 5.670, p = .029$) and Model 2 ($F(2, 17) = 6.833, p = .007$), however there is significant improvement in the prediction from Model 1 to Model 2 ($p(Fchange)Model2 = .022$). This suggests that the degree of activation in the left colour areas is most significantly predicated through inclusion of both the CLaN-L and CLaN-A scores of the synaesthetes (Model 2). The standardised β for CLaN-A is greater than that for CLaN-L, suggesting that although the inclusion of both variables generates the most accurate prediction of BOLD response, CLaN-A has the greatest impact on the prediction. In right hemisphere colour selective areas, both Model 1 ($F(1, 17) = 8.500, p = .010$) and Model 2 ($F(2, 16) = 4.517, p = .028$) are again significantly better for

the prediction of BOLD activation than a mean model, however the inclusion of CLaN-A in Model 2 is not a significant improvement on Model 1 ($p(Fchange)Model2 = .419$), therefore the most accurate prediction is made with Model 1 and CLaN-LT alone. The shrinkage (i.e. difference in variance explained by the data (R^2) and that which would be anticipated if the model were derived from the population ($R^2Adj.$)) of the final model is low in both left colour selective areas (6.6%) and right colour selective areas (3.9%). This suggests that the model should generalise well to a larger population and not be an effect of over fitting in this data set.

Together these results suggest that although both phenomenological aspects modulate the degree of colour selective response during synaesthetic conditions, CLaN-L has influences the activation in both hemispheres, whereas the inclusion of CLaN-A only provides a significant increase in predictive power in the left hemisphere. Interestingly, the standardised β for CLaN-A is greater than that for CLaN-L in the left hemisphere, suggesting CLaN-A has a greater overall influence than CLaN-L in the left hemisphere.

3.4.4 Exploratory analysis: Veridical colour processing

Exploratory analysis of veridical colour processing was conducted using the data obtained for the purposes of colour area localisation. This analysis was conducted to investigate group differences in acuity of colour discrimination between synaesthetes and controls, where synaesthetes have a significantly greater acuity in colour discrimination compared to controls, as demonstrated by the FMH test (Banissy, Cohen Kadosh, et al., 2009; Yaro & Ward, 2007). The activation response to coloured Mondrian (cMond) stimuli were contrasted with greyscale Mondrian (gMond) stimuli, with group level comparison between synaesthetes and controls at the whole-brain and ROI level. We also explored the role of individual differences in CLaN-L and CLaN-A synaesthesia phenomenology on veridical colour processing by conducting whole-brain and ROI regression analysis. All uncorrected data are reported here based on thresholds of $p < .005$ and extent of $k = 10$. Significant FWE corrected activation refers to a FWE corrected significance level of $p < .05$. Individual peaks are reported within a cluster if they are more than 8.0 mm apart. All anatomical landmarks are derived from the Automated Anatomical Labelling (AAL) toolbox for SPM (Tzourio-Mazoyer et al., 2002). All co-ordinates are stated in the MNI system.

In a between groups comparison, there were no significant differences between synaesthetes and controls in the response to physical colour in Mondrian stimuli. This suggests

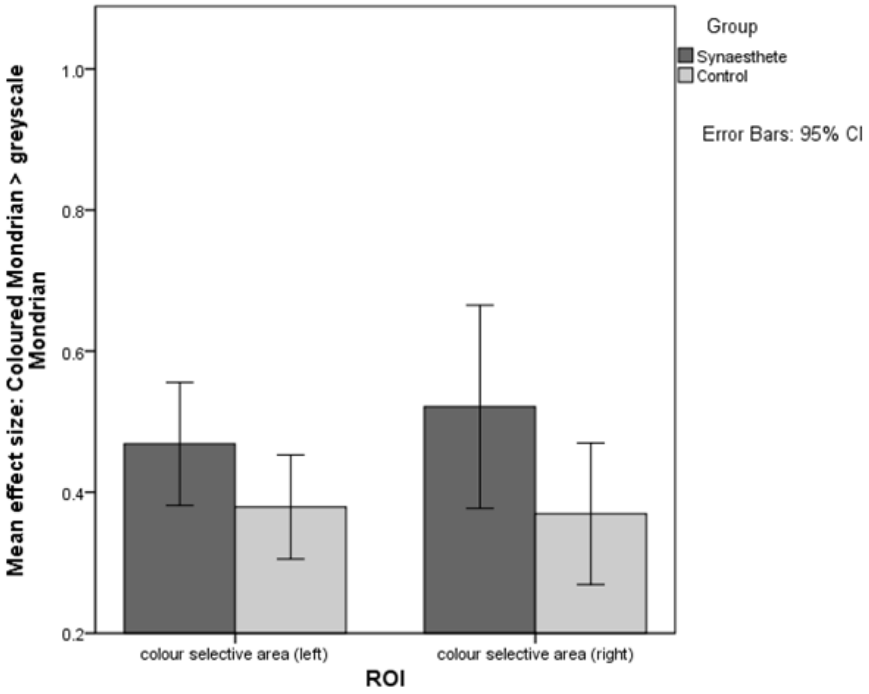


Figure 3.20: Activation within colour selective ROIs in the contrast of cMond>gMond. Effect sizes are SPM betas - a standardised effect size across conditions. The data demonstrate a significant response to colour within both left and right hemisphere ROIs in both synaesthetes and controls (left hemisphere: synaesthetes mean $\beta = 0.469, T = 11.246, p < .001$; controls mean $\beta = 0.379, T = 10.750, p < .001$; right hemisphere: synaesthetes mean $\beta = 0.521, T = 7.565, p < .001$; controls mean $\beta = 0.370, T = 7.703, p < .001$).

that at the population level there are no differences in the area or magnitude of response to physical colour between synaesthetes or controls, implying that veridical colour is processed similarly in terms of topographical organisation and magnitude of response in both groups.

Figure 3.20 shows the effect (SPM beta contrast values) in those areas identified as maximally responsive to colour in the contrast of cMond>gMond in each participant. In both synaesthetes and controls, these areas show a significant response to physical colour in both left (synaesthetes mean $\beta = 0.469, T = 11.246, p < .001$; controls mean $\beta = 0.379, T = 10.750, p < .001$) and right hemisphere colour selective ROIs (synaesthetes mean $\beta = 0.521, T = 7.565, p < .001$; controls mean $\beta = 0.370, T = 7.703, p < .001$).

Activations within these areas were assessed for normality in order to identify group level differences. There were significant deviations from normality in data obtained from the two ROIs (left colour, right colour) for both groups (total four data sets) in the

Table 3.7: Assessment of normality in ROI data on the contrast of cMond>gMond in untransformed and log (plus 1) transformed data. ∗significant at $p < .05$, ∗∗significant at $p < .01$, ∗∗∗significant at $p < .001$.

ROI	Group	zskew	zkurt	KS statistic	*p*(KS)	Levene's statistic	p(Levene's) Median
			Untransformed data				
Left colour areas	Control	0.343	2.404*	0.141	.200	0.386	.538
	Synaesthete	1.651	1.206	0.153	.200		
Right colour areas	Control	-1.796	2.589**	0.208	.024**	2.039	.161
	Synaesthete	0.940	0.740	0.142	.200		
			Log (plus 1) transformed data				
Left colour areas	Control	-0.923	2.354*	0.146	.200	0.056	.814
	Synaesthete	0.894	0.572	0.133	.200		
Right colour areas	Control	-3.339***	4.710***	0.259	.002**	1.029	.317
	Synaesthete	-0.586	1.410	0.147	.200		

contrast of cMond>gMond (see Table 3.7 for values). Specifically this included significant positive kurtosis in 2/4 and significant difference from a normal distribution in 1/4, as demonstrated by the KS test. Attempts were made to reduce the kurtosis through a log transformation (after the addition of 1 to each value to account for 0 and negative values). This transformation did not however bring all data into a normal distribution.

The distributions of the untransformed data are comparatively a closer approximation to normality than the transformed data. Violations of the assumptions of normality may lead to both false positives and false negatives in parametric testing, therefore results of such analysis will be interpreted with caution with and the aid of non-parametric tests where necessary.

Mauchly's test of sphericity was significant ($\chi^2(5) = 51.356, p < .001$), indicating that the variances of the differences between the ROIs are unequal; $\epsilon = .579$ therefore the Greenhouse-Giesser correction will be used in the assessment of effects of the ROI type.

A mixed ANOVA was conducted with the between subjects factor 'group' (synaesthetes and controls) and the within subjects factor 'ROI' (colour area left, colour area right). Analysis showed no significant main effect of ROI ($F(1, 38) = .294p < .591$) demonstrating that results obtained from each ROI are significantly different from each other. There a significant main effect of group ($F(1, 38) = 4.245, p = .046$), with synaesthetes ($M = 0.495, 95\%CI = 0.411 - 0.579$) showed slightly increased activation compared to controls ($M = 0.374, 95\%CI = 0.290 - 0.458$). There was no significant ROI-by-group

interaction ($F(1, 38) = .607, p = .441$), indicating that there was no significant difference between activation in the ROIs dependant on group membership. Planned comparisons demonstrated no significant difference between groups in left colour area activation ($t(38) = 1.643, p = .054$), however, there was a significant difference in right colour area activation ($t(38) = 1.806, p = .039$) with synaesthetes ($M = 0.521$) greater than controls ($M = 0.370$). Non-parametric analysis of group differences were assessed as there was evidence of violations of normality in both left and right colour areas. The Kruskal-Wallis test confirmed the results of the ROI-by-group interaction and demonstrated that there was no significant difference between activations in left colour areas ($\chi^2(1) = 2.273, p = .137$), or right colour areas ($\chi^2(1) = 2.723, p = .099$). These data demonstrate that there is a marginally significant group effect in response to veridical colour, with synaesthetes showing an overall increased response to colour across both ROIs.

Together, these ROI data demonstrate that there is no significant difference between synaesthetes and controls in colour selective areas in response to veridical colour. There is however a non-significant trend for increased activation in synaesthetes in colour areas, particularly in the right hemisphere. It should be noted that there is large variation in the response of synaesthetes to veridical colour across all ROIs, as demonstrated by the large 95% confidence intervals. We investigated and attempted to explain the source of this variation by regression of whole-brain and ROI data against measures of individual difference obtained in the assessment of synaesthesia phenomenology.

Individual differences Regression analysis was performed using the CLaN factors of localisation (CLaN-L) and automaticity (CLaN-A) as predictors of BOLD activation in contrasts of veridical colour processing (cMond>gMond). A FWE corrected significant cluster of activation was found in the opercular part of the right inferior frontal gyrus (OperRIFG) in the contrast cMond>gMond against CLaN-A [48, 12, 12] ($k = 419, p(FWEcluster) = .0121, Z = 3.740, p(FWEpeak) = .977; R = .816, R^2 = .666, R^2Adj = .647, b = .020, \beta = .816, t(18) = 5.991, p < .001, F(1, 18) = 35.888, p < .001$) (see Figure 3.21 and Figure 3.22). This area shows a significant positive relationship with the CLaN-A measure, that is activation in this area is significantly predicted by individual differences in automaticity of the synaesthetic concurrent, with greater activation predicted by greater automaticity.

In regression analysis of colour area ROIs there were no significant relationships between colour selective area activation and CLaN-A or CLaN-L in cMond>gMond (colour area left: (CLaN-A) $R = .079, p = .370$, (CLaN-L) $R = .266, p = .128$; colour area right:

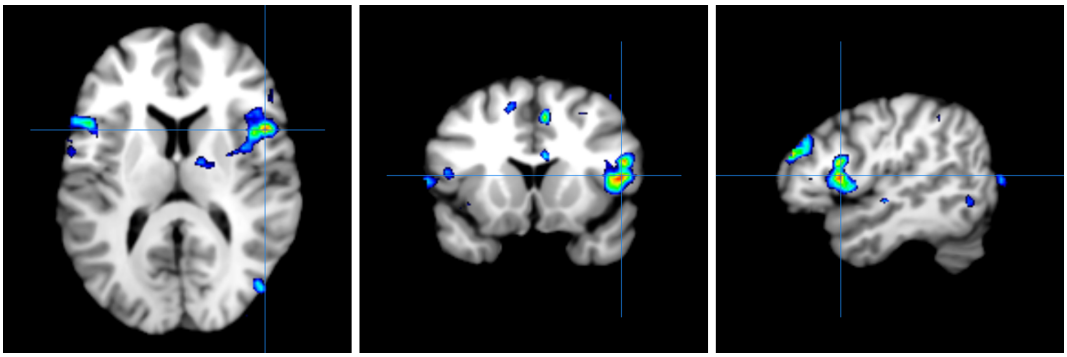


Figure 3.21: FWE corrected significant cluster in the right inferior frontal gyrus following whole-brain regression of 2nd level synaesthetes data in the contrast of cMond>gMond with regression against CLaN-A [48, 12, 12] $k = 419, p(FWEcluster) = .0121, Z = 3.740, p(FWEpeak) = .977$

(CLaN-A) $R = -.054, p = .410$, (CLaN-L) $R = .198, p = .202$). Thus it appears that activation in the inferior frontal gyrus under veridical colour conditions is related to individual differences in synaesthesia phenomenology, whereas activity in colour areas themselves is not predicted by phenomenology.

These exploratory analyses of veridical colour processing in synaesthetes suggest at the group level there is no significant difference between synaesthetes and controls, in whole-brain or ROI analysis, although there is a trend for increased response to veridical colour in colour selective ROIs for synaesthetes. We also demonstrate that the degree of activation in the OperRIFG during veridical colour processing is significantly predicted by the automaticity of synaesthetic concurrents.

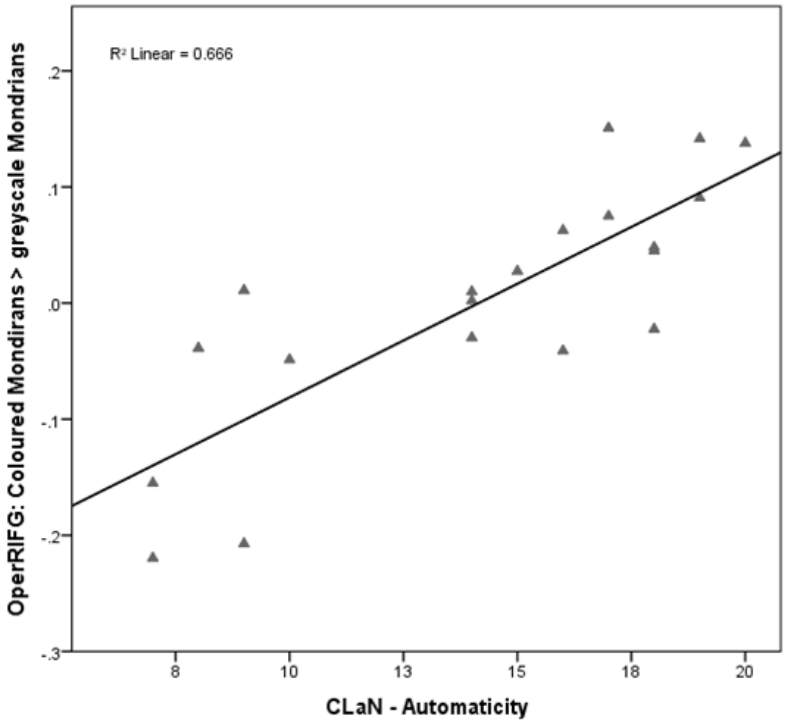


Figure 3.22: Regression of the FWE corrected significant cluster in the right inferior frontal gyrus in the contrast of cMond>gMond with the CLaN-A results.

3.5 Discussion

A number of areas are consistently reported in fMRI investigations of synaesthesia, however, there have been conflicting results regarding activation of 'real colour areas' during the synaesthetic colour experience (Rouw, 2011). The source of this variation has been suggested to lie in methodological differences, particularly in the sensitivity of analysis, however, there has been no systematic investigation regarding the extent to which individual differences in phenomenology may impact this important result. We sought to address the impact of individual differences in synaesthetic phenomenology on the response of colour selective areas under synaesthetic conditions, with the hypothesis that the greater the degree of localisation of the concurrent (CLaN-L), the greater the degree of the response to synaesthetic colour. Colour selective areas were identified with an independent functional localiser, and we assessed individual differences using a continuous (rather than dichotomous) measures of phenomenology. These measures included a newly defined aspect of automaticity in synaesthetic concurrents (CLaN-A), which was used in exploratory whole-brain and ROI regression analyses.

In accordance with our hypothesis, our data demonstrate that the greater the localisation of the synaesthetic concurrent, the greater the degree of activation in both left and right colour processing areas. Exploratory analysis of the impact of individual differences in CLaN-A did not accord with our tentative hypothesis regarding a relationship with frontal attention areas, however CLaN-A was found to predict activation in a region of the right middle occipital gyrus under synaesthetic conditions. In further exploratory analysis, the individual differences in CLaN-A scores were included in a two stage predictive model of colour area activation, along with CLaN-L. This two stage model demonstrated that the response in left colour areas under synaesthetic conditions was most significantly predicted by taking into account the independent measures of both CLaN-L and CLaN-A. In right the right colour areas, response to synaesthetic colour was predicted by CLaN-L alone. Exploratory analysis was also conducted on veridical colour processing, to investigate the increased acuity in hue detection reported in synaesthetes compared to controls. Here, synaesthetes showed a trend for increased responsiveness to veridical colour in colour selective ROIs, and individual differences in CLaN-A predicted the degree of activation in the OperRIFG. We discuss the nature and impact of these results below, and make predictions regarding how the exploratory analyses could be used to motivate further investigations.

3.5.1 Synaesthetic colour processing

In analysis of the synaesthetic colour condition, no evidence was found for group level activation in or near to colour areas, in whole brain or ROI analysis (see Figure 3.17). However, regression analysis with measures of individual differences in GCS phenomenology, demonstrated that activity in the left colour area was significantly predicted by a two stage hierarchical regression model with predictors CLaN-L (1) and CLaN-A (2). In right colour areas, activation was predicted by CLaN-L only. This data represents the first clear demonstration that the degree of colour area response to synaesthetic colours may be modulated by the nature of the individual synaesthetic phenomenology, suggesting that previous conflicting reports of colour area activation may be confounded by the choice of participants rather than the method of analyses employed.

The demonstration of a BOLD response in 'real' colour areas lead to a significant advance in GCS research, as it provided objective verification of the subjective response. Later attempts to replicate this effect have not always been successful, and consequently cast doubt on the perceptual nature of the GCS experience. Examination of the experimental cohorts in successful and unsuccessful replications of this key result lead to the hypothesis that individual differences in synaesthetic phenomenology may have contributed to the group level results reported, a hypothesis which was supported by our regression analysis on BOLD activation against two independent measures of synaesthetic phenomenology. Where previous investigations have used the limited phenomenological descriptors of 'projector' and 'associator', our regression analysis applied the newly developed measures of localisation of synaesthetic concurrent (CLaN-L) and automaticity of the concurrent experience (CLaN-A). as described by Rothen, Seth, et al. (2013), these measures offer a significant improvement over the projector-associator scale as they are developed following the rigorous statistical analysis required to validate such a first-person measure. We also note that the CLaN factors are continuous, rather than categorical, and are therefore amenable to parametric analysis. Whilst our hypothesis was formed on the basis of observations on the projector-associator scale, we recognise that PA and CLaN-L phenomenology are not equivalent and cannot be treated interchangeably. We demonstrate that CLaN-L and the standard PA measures of ISEQ and RS-PA are significantly correlated, but note that our observed correlation between phenomenology and BOLD response was uniquely identifiable through analysis of the CLaN-L measure alone.

The localisation of a concurrent according to the CLaN-L measure refers to the degree to which a synaesthete reports to see colours in a specific location. That location need not

be externalised (cf. 'projectors', who report to see a concurrent in external space), but those scoring high on CLaN-L do report their concurrent to be more 'perceptual' and vivid rather than associative. We have shown this experience to predict the degree of activation in colour selective areas under synaesthetic conditions, suggesting the phenomenological experience and neural activity are related. This relationship may be similar to that of vividness of a memory during recall and the degree of hippocampal activation during encoding and retrieval, where more vivid memories are predicted by greater hippocampal activation (Wais, 2008).

The relationship between the vividness of a synaesthetic colour and the degree of colour area activation may be intuitive. Less clear, however, is how the automaticity (CLaN-A) of the concurrent experience may translate into the degree of activation. Our exploratory analysis suggests that those synaesthetes who have a highly automatic colour experience (that is, they do not need to purposefully direct their attention toward their synaesthesia in order to experience a concurrent) also have a high degree of colour area activation, but only in the left hemisphere. The localisation and automaticity factors are statistically independent, such that an individual may have localised concurrents, but they are not experienced with a high degree of automaticity. The automaticity of the experience may relate therefore to attentional processes, perhaps top-down direction of attention.

Although the CLaN measures have identified significant and informative relationships between subjective experience and neural activity, further development is required in our description of the localisation and automaticity factors. Behavioural validation of the automaticity factor may be achieved through investigation of priming effects, for example we may expect to see pop-out or break through effects for colour stimuli to be correlated with CLaN-A. We may also seek to more fully understand the phenomenological experience addressed in the CLaN-L and CLaN-A questions through Elicitation Interview or other second-person measures (see Chapter 2). We may specifically seek to determine where CLaN-L differs from alternative PA dimensions. A possible source of variation in between CLaN-L and alternate PA measures may be suggested in the exploratory regression analysis of CLAN-L against whole brain activations during synaesthetic conditions, specifically in the supplementary motor area response. Precentral and preparatory motor area activation has been previously demonstrated in investigations of synaesthesia (e.g. Laeng, Hugdahl, and Specht (2011); Nunn et al. (2002); Rouw and Scholte (2010); Weiss et al. (2005)) and these have been suggested to relate to "sensing of and acting on the outside world" (Rouw et al., 2011, p. 227). Our finding here of increased SMA activ-

ation in those synaesthetes with localised concurrents supports this hypothesis, where a localised concurrent promotes greater activation of a motor response, even when no motor response task was employed. In the wording of the CLaN-L questions however, we find items relating to active engagement with the external environment, such as "I can *point* to the location of the synaesthetic colour", and similarly, "I can *choose to alter* the location of the synaesthetic colours" (emphasis added). Less active questioning is used in the RS-PA or ISEQ questionnaires, which may account for the specificity in CLaN-L regression relationships.

The CLaN-A and CLaN-L measures have demonstrated previously unreported lateralisation effects in colour area response, which warrant further investigation. Where synaesthetic colour area activation has previously been reported, there has been little consistency in lateralisation of this effect. For example, Nunn et al. (2002) reported left hemisphere V4 in synaesthetic conditions and right hemisphere V4 in veridical colour conditions. The authors suggested that this left/right split was the result of re-wiring, where the left hemisphere V4 was employed solely in the processing of synaesthetic colours. However, based on the present data, we may again propose that this left/right differentiation reflected individual differences in the synaesthetes, where left hemisphere activation is related to automaticity and localisation and the right hemisphere is related to the localisation only.

3.5.2 Veridical colour processing

In our exploratory analysis of veridical colour processing, we show that synaesthetes have a trend for increased response to veridical colour in (see Figure 3.20). This increased responsiveness may relate to the reports of increased colour acuity in GCS, as denoted by significantly improved FMH accuracy scores in synaesthetes compared to controls. Future investigations of veridical colour processing in GCS may use FMH directly on a case wise basis in order to assess the impact of individual differences in colour area activation under veridical colour conditions and hue acuity. In whole brain regression analysis, we found activation the OperRIFG was modulated by individual differences in CLaN-A during veridical colour processing.

The OperRIFG is classically implicated in inhibitory control such as go/no-go and stop signal tasks (e.g. Aron, Dowson, Sahakian, and Robbins (2003); Menon, Adleman, White, Glover, and Reiss (2001)). More recently however, the role of the OperRIFG in inhibitory control has been proposed to relate to the detection of important or salient cues as it shows activation under both cue counting, cues which initiate a response and cues which signal

the inhibition of a response (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). The OperRIFG has therefore been ascribed a functional role in the detection of cues which are relevant to the current task demands (Hampshire, Thompson, Duncan, & Owen, 2009). This suggests that in those synaesthetes who report an automatic concurrent experience which requires little attention to the inducer, veridical colour is responded to as though it is an important or salient stimulus. This may account in part for why these individuals are aware of their concurrent colour experience with little focused attention, as important or salient cues are normally found to break through into consciousness with little directed attention. This finding may also have implications for the development of synaesthesia, as and attentional bias towards colour may impact learning strategies.

Terhune, Tai, Cowey, Popescu, and Cohen Kadosh (2011) suggest that GCS may result from hyper-sensitivity in the concurrent processing stream, as synaesthetes demonstrated a 300% lower phosphene threshold[5] compared to controls over primary visual areas (Terhune et al., 2011). Terhune et al. (2011) suggest that at an early age an enhanced cortical excitability might lead to an increase in domain specific processing, i.e. a hyper-sensitivity to colour (Terhune et al., 2011). A selective enhancement of colour processing at an early age is also suggested by Watson, Akins, and Enns (2012) who found second order associations between colour and letter shape, frequency and ordinality in synaesthesia are in common with other strategies on the use of colour (Watson et al., 2012). For example, they found that letter frequency was most often mapped to differences in concurrent luminance. Both letter frequency and luminance can be expressed as continuous measures, whereas letter shape and ordinality have categorical distinctions and accordingly map to variations in hue[6] These findings suggest a strategic association of colours to letters during development, potentially as a result of an increased propensity for colour domain processing due to enhanced cortical excitability, as proposed by Terhune et al. (2011). We suggest that the hypersensitivity of synaesthetes to colour experience is reflected in

[5]The phosphene threshold is used as a measure of cortical excitability. It refers to the intensity of magnetic stimulation that is required to induce an illusory flash of light

[6]these are referred to as second order relationships as they describe a correlation between two relations, such that a relationship in one domain (e.g. relative letter frequency of 'A' verses 'B') is related to a correlation in a colour domain (e.g. differences in luminance between two colours). Watson *et al* find that individual synaesthetes may apply colour-letter mapping rules interchangeably, for example, for one subject the concurrent for A may be mapped according to its frequency, where a high frequency relative to Z would lead the concurrent for A to have a higher luminance compared to Z, but the letter B might be mapped according to ordinality with respect to C, where its proximity to C would promote a concurrent colour with low difference in hue to C.

their trend for increased colour area response to veridical colour, and specifically that an attentional bias towards colour may be observed at a group level, with individual differences in bias predicated by cortical excitability. Such a research program would be well supported by the exploratory results reported here.

3.6 Conclusions

This investigation has demonstrated that individual differences have a significant impact on neural activity in GCS. We importantly demonstrate that the conflicting results on activation of real colour selective areas during synaesthetic conditions is due to modulation of colour area response by independent factors of localisation and automaticity of concurrents. We find lateralisation of the response to synaesthetic colour, with activation in left hemisphere colour areas modulated by both localisation and automaticity, whereas right hemisphere areas are modulated by localisation alone. We also report the results of exploratory analysis of veridical colour processing and suggest that activity in the OperRIFG under non-synaesthetic conditions relates to the automaticity of the concurrent during synaesthetic conditions, such that synaesthetes process colour as an important or salient stimulus.

This is the first investigation to assess effects of a novel description of the projector-associator measure along a localisation dimension rather than in internal-external dimension. This is also the first investigation to assess individual differences in automaticity of concurrents in GCS. In doing so, we have demonstrated that individual differences in localisation predict the degree of colour area activation across both hemispheres, as hypothesised. Our exploratory analysis also revealed that automaticity predicts colour area activation in the right hemisphere. We suggest that such measures should be employed in future investigations of GCS, whilst we continue to develop suitable phenomenological descriptors of the GCS experience, and that group level analysis should be complemented by suitable regression to control for the effects of individual differences.

Chapter 4

Functional connectivity in grapheme-colour synaesthesia assessed through psychophysical interactions

4.1 Chapter summary

In psychophysical interactions (PPI) analysis, functional connectivity is assessed under different experimental states, to determine how the temporal correlations vary with the psychological context. In this Chapter, we test the hypothesis of van Leeuwen et al. (2011) that both projector-like and associator-like synaesthetes feature functional connectivity between the superior parietal lobe, colour areas and letter areas, but that this connectivity is modulated by individual differences in phenomenology. We assess PPI functional connectivity analysis between synaesthetes and controls, to determine whether the proposed network is trait specific. We also conduct whole-brain regression analysis on functional connectivity patterns, to test the hypothesis that the degree of localisation of a concurrent is related to the degree of bottom-up network connections. Exploratory analysis is also conducted on group-level and individual differences in functional connectivity during veridical colour processing, using colour area and OperRIFG seeds.

In synaesthetic colour processing, there was no evidence of group differences in functional connectivity between the parietal seeds and any other area of the brain, nor between colour areas and the rest of the brain. Colour area connectivity was modulated by CLaN-L such that there was increased connectivity between right colour areas and a cluster in the cuneus with increased CLaN-L scores. These data suggest that the connectivity model proposed by van Leeuwen et al. (2011) is not trait specific, and that the proposed projector-associator differences are not identifiable as functional connectivity differences between colour and letter areas related to CLaN-L scores, although this is generally supportive of the involvement of low level processing areas, as suggested by Terhune et al. (2011).

In exploratory analysis of veridical colour processing, synaesthetes had a reduced network involving left hemisphere colour areas compared to controls, but increased coupling between the OperRIFG and primary visual areas, along with areas related to self-relevant information processing. We speculate that the reduced engagement of left colour areas contributes to the trend for increased responsiveness of synaesthetes relative to controls in right colour area activity, and suggest that the coupling between OperRIFG and primary visual areas may lead to an increase in perceptual brightness of coloured stimuli for synaesthetes. We propose an experiment to test this hypothesis through a luminance-matched discrimination task.

4.2 Introduction

4.2.1 Concurrent induction models in grapheme-colour synaesthesia

Present theories in synaesthesia ascribe the trait to result from differences in functional or structural connectivity (the cross-wiring hypothesis) or differences in effective connectivity (the disinhibited feedback hypothesis). Structural differences in connectivity of synaesthetes has been demonstrated indirectly by increased grey matter in the temporal lobe, specifically in the area of the fusiform gyrus FG, encompassing the visual word form area (VWFA) and colour processing area V4 (Jäncke et al., 2009; Rouw & Scholte, 2007; Weiss & Fink, 2009). Direct structural connectivity has also been implicated in studies employing diffusion tensor imaging (DTI), where increased fractional anisotropy (FA) has been demonstrated in synaesthetes relative to controls in the right inferior temporal cortex, next to the FG (Rouw & Scholte, 2007) and roughly in the area of V4 (Jäncke et al., 2009). It should be noted, however, that a large number of the findings of Jäncke et al. (2009) only reached statistical significance under low and uncorrected thresholds, therefore the 'cross-wired' state suggested by these structural differences may not be present in all synaesthetic individuals.

There has been limited investigation into differences in functional connectivity of synaesthetes, aside from the preparatory work involved in the construction of a dynamic causal modelling (DCM) investigation of van Leeuwen and colleagues (van Leeuwen, den Ouden, & Hagoort, 2010; van Leeuwen et al., 2011). In PPI analysis of functional connectivity, van Leeuwen, den Ouden, and Hagoort (2010) demonstrated coupling between a superior parietal lobe (SPL) seed and target areas in the left fusiform gyrus and bilateral middle occipital gyrus. van Leeuwen, den Ouden, and Hagoort (2010) found all three of these targets to lie within "areas involved in real colour processing", reaching significance after a small volume correction [ibid.] . The V4 seed, by contrast did not show coupling with the SPL, rather there was effective connectivity with the left middle frontal gyrus, anterior cingulate and right inferior frontal gyrus. These PPI results were then taken forward into effective connectivity DCM analysis. Although the functional connectivity analysis showed no main effect of projector-associator group membership, the effective connectivity analysis suggested that projectors showed 'bottom-up' connectivity, with activation in a 'letter shape area' (LSA) of the FG driving V4 activation, and representations of both colour and letter form being bound in the SPL. The DCM evidence for associators more closely resembled a 'top-down' process, where the FG drives the higher SPL areas and the SPL in turn drives V4 activation (van Leeuwen et al., 2011). The authors con-

clude that these investigations generally demonstrate that the same network of areas are responsible for the synaesthetic experience (V4, LSA and SPL), but the subjective nature of the experience on the projector-associator scale modulates effective connectivity within that network.

The PPI results reported in van Leeuwen, den Ouden, and Hagoort (2010) are based on analysis of synaesthetes alone, rather than in comparison between synaesthetes and controls. Thus the functional and effective connectivity patterns reported may not relate to the synaesthetic trait specifically, as differenced from controls, but rather may relate to the experimental context alone and be present in both populations. We also note that the targets reported in van Leeuwen, den Ouden, and Hagoort (2010) are significant only at $p < .001$ uncorrected threshold, and thus may represent false positives in this voxel wise analysis. Another significant limitation of these studies is the use of the PA scores as a continuous measure through differencing the scores obtained in the two categories. As discussed in Chapter 3, the PA questionnaire was designed for dichotomous grouping of synaesthetes, but the questionnaire itself has not been rigorously validated (Rothen, Tsakanikos, et al., 2013). It should also be noted that in their assessment of participants, van Leeuwen et al. (2011) reported that 6 of their participants experienced their concurrents in peripersonal space, but not in the same location as the concurrents. van Leeuwen et al. (2011) classified these participants as "mental screen projectors", forming an intermediary cluster in the PA difference score. As discussed in Chapter 3, the PA questionnaire was designed specifically to classify participants as having either projector *or* associator like experiences. The formation of this intermediary cluster in van Leeuwen et al. (2011) is evidence to support our hypothesis that a continuous phenomenology measure may be more appropriate in the description of this trait, however to do so requires the application of a tool which has been specifically designed to generate continuous scores, such as the CLaN.

An alternate model to top-down and bottom-up models of concurrent induction has been proposed by Terhune et al. (2011). Terhune et al. (2011) suggest that GCS may result from hyper-sensitivity in the concurrent processing stream, as synaesthetes demonstrated a 300% lower phosphene threshold[1] compared to controls over primary visual areas (Terhune et al., 2011). Terhune et al. (2011) suggest that at an early age an enhanced cortical excitability might lead to an increase in domain specific processing, i.e. a hyper-sensitivity to colour (Terhune et al., 2011). Although this model does not speak

[1]The phosphene threshold is used as a measure of cortical excitability. It refers to the intensity of magnetic stimulation that is required to induce an illusory flash of light

directly to connectivity theories of GCS, it does suggest a strong influence of low level visual activity, supporting the bottom-up connectivity models.

In this Chapter, we address the unresolved issue of differences in functional connectivity which are specific to synaesthesia, that is, differences which are evident when comparing the functional connectivity patterns of synaesthetes to a control population. We use the psychophysical interactions (PPI) method, developed by Friston et al. (1997)and colleagues to investigate functional connectivity between brain regions, through assessment of the modulatory role of psychological stimuli on regional correlations in fMRI activity. This technique was one of the earliest developed methods of assessing functional connectivity and is an extension of the classical general linear model (GLM) approach.

4.2.2 Functional connectivity analysis through psychophysical interactions (PPI)

PPI involves the definition of a GLM design matrix with a regressor of interest modelling the interaction of a physiological variable (seed time course) and a psychological variable (experimental condition). Fitting the GLM to the interaction term will then identify regions in a voxel-wise manner which respond to the experimental condition when and only when activity in the seed region is high. In essence, this analysis assesses temporal correlations between areas which also vary with the experimental condition. This identifies coupling between areas which is high under the condition of interest, but low during other conditions. This coupling can be interpreted to demonstrate that either (i) the influence of the seed on the target is modulated by the experimental condition, or (ii) the response of the target to experimental condition is modulated by the seed (Friston et al., 1997). The parameter of the regression slope in the target area (β) represents the influence of the interaction under those conditions. A statistical parametric map is generated for all voxels in the fMRI image by testing the significance of β against the null hypothesis that $\beta = 0$. If β is significantly different from 0 in an area, we can conclude that activation in this area is influenced by the interaction between the seed and the experimental condition. Similarly where β is not significantly different from 0, we can say that under those conditions there is no stimulus specific interaction with the seed area.

The functional connectivity model of PPI is a simple, linear interaction. There is no self connection in the model and connectivity is not *assumed* to be symmetrical (unlike in simple correlations). The inputs to the model (i.e. the physiological and psychological time courses) are assumed to sum linearly in forming the interaction term and the con-

nection strengths are fixed, although they may show time-dependent changes. Friston and colleagues note that "these are strong and unrealistic assumptions [for a complex neural model], but they have proved useful in making the analysis of [functional] connectivity more robust and tractable, particularly in relation to multiple regression approaches" (Friston et al., 1997, p.219-220) (e.g. Friston, Frith, and Frackowiak (1993)). In building the PPI design matrix, both the physiological and psychological variables are retained as regressors of no interest. Their inclusion removes any variance which can be accounted for as a main effect of the physiological variable (e.g. other regions which show a similar time course as the seed region and thus show physiological correlations) or a main effect of the psychological variable (which would be a repetition of the standard GLM stimulus contrast for that condition). Any variance which is not related to these main effects can then be said to represent context specific influence between the seed and target. The PPI model is built individually for each participant to gain first level results. Second level random effects design matrices can be built separately for each experimental group and two-sample t-tests conducted to assess group differences in regional coupling.

PPI has previously been applied to investigate modulation of fMRI activation in both conscious, cognitive task manipulations and unconscious processes. For example, Hariri, Bookheimer, and Mazziotta (2000) used PPI to investigate differences in response to face stimuli when participants were tasked to perform either a perceptual matching task or an 'intellectual' task of decoding the portrayed emotion. In both tasks, fearful stimuli were associated with amygdala activation, but this was reduced in the intellectual task compared to the perceptual task. In the intellectual condition, amygdala activation was also shown to have connectivity with right prefrontal cortex. The authors suggest that this amygdala-prefrontal connectivity demonstrate a modulation of the emotional experience (an attenuation of the affective response) through interaction with higher cognitive areas, having implications for our understanding of emotional response by context (Hariri et al., 2000). Elsewhere, PPI has been applied to in the study of mechanisms of pain response, where it has been demonstrated that under placebo conditions the rostral anterior cingulate cortex shows increased connectivity with subcortical structures involved in conditioned responses (amygdala and periaqueductal gray) (Bingel, Lorenz, Schoell, Weiller, & Büchel, 2006). More broadly, PPI has also been used to investigate hemispheric specialisation. Stephan and colleagues demonstrated through PPI that laterality in fMRI activation is dependent on task context as opposed to laterality in stimuli presentation, and that connectivity relating to areas involved in cognitive control was limited to the

hemisphere recruited for the task (Stephan et al., 2003). Together, these investigations demonstrate the varied applications of PPI and in particular how they can be used to resolve issues of task dependent activation in a manner which may be particularly informative when interpreted in conjunction with the classical GLM approach, where classical GLM is used to interpret the role of the seed area and PPI demonstrates its influence on other brain regions.

Other methods of functional connectivity analysis include data driven assessments such as principle components analysis (PCA) and independent components analysis (ICA). Both these methods decompose the whole-brain signal into a number of linearly uncorrelated time courses (components), which contain regions which are functionally correlated with each other, but are independent of the other components if the whole-brain data are normally distributed (McKeown et al., 1998). Such methods are more commonly applied in exploratory analysis of resting state data, where there is no experimental manipulation and therefore no explicit hypothesis being tested. PPI and DCM are, by distinction, model driven, as they require *a priori* selection of seeds which are hypothesised to be or relevance to the connectivity network of interest. In the case of DCM, models are generated to define each region as a source or target in the network, thus directional (effective) connections can be determined on the basis of Bayesian model selection (Friston, Harrison, & Penny, 2003). Structural equation modelling (SEM) is similarly data-driven in that ROIs are defined *a priori*, however, the connections or direction of connections are not specified, unlike in DCM, rather graph theoretic measures are used to determine the relative weights of connections. SEM algorithms search through all possible connection strengths until the weights are determine for each which best fit the data (Büchel & Friston, 1997).

The most appropriate mode of connectivity analysis applied in any given investigation is dependent on the hypothesis in question. In this Chapter we will use PPI as this method forms the basis of the effective connectivity network presented in van Leeuwen et al. (2011). We will use PPI to identify functional connectivity networks present during synaesthetic colour processing, to test the hypothesis presented in van Leeuwen et al. (2011) that parietal and colour area connectivity is central to the classical bottom-up and top-down connectivity hypotheses of synaesthesia. Importantly, however, we will assess connectivity differences between synaesthetes and controls through a two-sample t-test of whole brain connectivity maps, to determine whether this trait specific. We will assess functional connectivity using parietal and colour areas as seeds, as in van Leeuwen et al. (2011), and investigate the effects of individual differences in phenomenology, but use the newly

developed CLaN measures of localisation and automaticity (Rothen, Tsakanikos, et al., 2013) rather than the discontinuous projector-associator measure. Application of this continuous measure enables parametric regression analysis to be performed on the whole brain, to identify coupling between areas which is modulated by the phenomenological measure. If the group differences in activation identify parietal and colour area coupling as in van Leeuwen et al. (2011), it is hypothesised that the regression analysis against CLaN-L will identify a region in the left fusiform gyrus which is differentially connected to colour or parietal areas depending on projector or associator grouping, relating to the LSA of van Leeuwen et al. (2011) [2]. CLaN-L has a significant positive relationship with PA measures (see Chapter 3), however, they are not equivalent measures and as such should not be expected to produce equivalent results. CLaN-L and PA differ particularly in their differential scoring in associators (some associators may be high localisers), however there is greater continuity in their scoring at the projector end of the scale (high projectors are necessarily high localisers). We may therefore expect to see a greater degree of agreement with CLaN-L positive regressions (relating to projector traits) and the results of van Leeuwen et al. (2011) than with CLaN-L negative regressions (relating to associator traits) and the results of van Leeuwen et al. (2011). Accordingly, it is hypothesised that the CLaN-L related functional connectivity will show a positive relationship with coupling between the fusiform gyrus and colour area seeds, and potentially a negative relationship with coupling between the fusiform gyrus and parietal seeds.

We will also conduct exploratory analysis of the context specific functional connectivity present in veridical colour processing, using seeds of individually defined colour selective areas and the OperRIFG, identified in relation to individual differences in CLaN-A in Chapter 3. This analysis will shed light on the trend for increased colour area response and activation in the right inferior frontal gyrus identified in synaesthetes compared to controls in GLM analysis of veridical colour processing, which we hypothesis to suggest that synaesthetes respond to colour as an important or salient stimulus. This analysis will be applied in group comparisons of both synaesthetes > controls, controls > synaesthetes, along with individual differences in synaesthetes modulated by CLaN-L and CLaN-A.

[2] Although we will not functionally localise the letter shape area, we will conduct small volume correction on the relevant connectivity maps using a left fusiform gyrus mask, following the definition of the LSA used in van Leeuwen et al. (2011) as an area in the fusiform gyrus involved in the analysis of complex and abstract shapes, such as graphemes (Dehaene, Cohen, Sigman, & Vinckier, 2005)

4.3 Methods

The data analysed in this Chapter are the same data analysed in the Chapter 3, obtained from the same participants in the same scanning session. Brief experimental details are provided below, for reference. For complete details of participants and methods, please see Chapter 3.

4.3.1 Participants

The conduct of this project was approved by the Research Governance and Ethics Committee for Brighton and Sussex Medical School (Project Approval Reference: 10/049/GOU). Participants were 20 grapheme-colour synaesthetes and 20 controls, matched for age, gender, handedness and education level, as described in Chapter 3 (Section 3.3.1). Synaesthesia was confirmed through completion of the online synaesthesia battery (Eagleman et al., 2007) with all synaesthetes falling within the range of acceptable scores in consistency in concurrent colour selection after transformation to perceptual CIELUV colour space (Rothen, Seth, et al., 2013) (see Section 3.4.1.3). All participants took part in prescreening for MRI safety, reported no history of physiological or psychological trauma and had normal colour vision. Control participants additionally reported no synaesthesia of any form for themselves or 1st and 2nd degree relatives. Synaesthetes and control participants underwent a single fMRI scanning session. Synaesthetes completed the CLaN synaesthesia phenomenology questionnaire (Rothen, Tsakanikos, et al., 2013), being scored on their localisation (CLaN-L) and automaticity (CLaN-A) of concurrents, as described in Section 3.3.3 and Section 3.4.1.

4.3.2 fMRI

Data were acquired at the Brighton and Sussex Medical School, Clinical Imaging Sciences Centre using a Siemens Avanto 1.5T system. A T1 weighted structural image was acquired (TR 1160 ms, TE 4.44 ms, flip angle 15°, voxel size 0.9 x 0.9 x 0.9 mm, 192 slices, 0.45 mm slice gap) followed by an echo-planar imaging (EPI) sequence for functional volumes (TR 2210 ms, TE 30 ms, flip angle 90°, voxel size 3 x 3 x 3 mm, 36 slices, 0.75 mm slice gap). The initiation of visual stimuli presentation was locked to the acquisition of the 6th volume, to allow for T1 saturation effects.

fMRI data were acquired in separate runs for 1) colour area localisation, and 2) investigation of synaesthesia effects, as described in Sections 3.3.4.2 and 3.3.4.3 respectively. Stimuli for the colour area localiser included coloured and greyscale Mondrian-type im-

ages, displayed in six alternating blocks of coloured and greyscale stimuli in a single run, with 84 trials per condition (14 trials per block, displayed for 1000 ms, separated by a 500 ms grey isoluminant screen) and a total run duration of 252 s (see Figures 3.3 to 3.5). Stimuli for the synaesthesia conditions included inducing graphemes (letters) coloured black (letters black - lb), non-inducing graphemes (punctuation symbols) coloured black (symbols black - sb), inducing graphemes coloured congruently with synaesthetic concurrents (letters coloured congruently - lcc) and inducing graphemes coloured incongruently with synaesthetic concurrents (letters coloured incongruently - lci) and coloured non-inducing graphemes (symbols coloured) (see Figure 3.6). Stimuli were displayed in condition blocks, with five blocks of each condition per run and four runs completed for each participant, furnishing 240 trials of each condition (12 trials per block, stimuli displayed for 2000 ms, separated by a 50 ms grey isoluminant screen) (see Figures 3.7 to 3.8). Control participants viewed exactly the same stimulus as their matched synaesthete.

4.3.3 Seed selection

PPI effective connectivity analysis was conducted following the method of Friston et al. (1997). Seeds were selected to assess coupling between colour areas, and parietal areas related to the binding of the synaesthetic and veridical percepts (see Table 4.1). Colour areas included individually defined colour selective areas in left and right hemispheres, identified as described in Section 3.3.6.2. Briefly, individual colour selective areas were identified as the area within the occipital lobe of each subject which showed greatest response to colour Mondrian stimuli relative to greyscale Mondrian stimuli. Parietal seeds were identified as those areas which showed significantly increased response the interaction between group and synaesthetic induction (synaesthetes[lb>sb] > controls[lb>sb]) and were consistent across all synaesthetes (i.e. did not show variation with individual differences in phenomenology). These areas are believed to relate to the binding of the synaesthetic and veridical percept. In exploratory analysis of veridical colour processing, seeds included the individually defined colour selective areas and a further seed in the OperRIFG to assess the functional connectivity of this area in the suggested processing of veridical colour as an important or salient stimulus.

4.3.4 Physiological, psychological and interaction variables

Physiological, psychological and interaction variables were created with using SPM5 batch scripts (Wellcome Trust Centre for Neuroimaging, 2005). The physiological time course

Table 4.1: Co-ordinates of seed areas applied in PPI analysis along with a description of how these seeds were identified in the GLM analysis of Chapter 3. Participant colour selective areas were defined individually, therefore the mean co-ordinates for each group are provided here for comparison.

Seed Name	x	y	z	Description
Left colour areas:				Individually defined colour selective areas in the left (pxV4_l) and right (pxV4_r) hemisphere for each participant. Defined as the maximally responsive peak in the occipital lobe to the contrast of coloured Mondrians > greyscale Mondrians.
mean syn.	-22	-83	-5	
mean control	-25	-72	-3	
Right colour areas:				
mean syn.	24	-81	-3	
mean control	15	-83	-5	
Inferior parietal (L)	-46	-48	50	Areas with significantly greater response in synaesthetes relative to controls in the contrast of inducing black letters > non-inducing black symbols (lb>sb).
Inferior parietal (R)	44	-48	48	
Precentral (L)	-46	4	34	
OperRIFG	48	12	12	Area of activation in coloured Mondrians > greyscale Mondrians in (synaesthetes only) which is significantly predicted by automaticity of synaesthetic concurrents (CLaN-A).

was extracted from 8 mm radius spherical ROIs, centred on the seed co-ordinates listed in Table 4.1. Time course data consisted of the first scaled eigenvariate of the ROI (i.e. the weighted mean). Time course data were extracted for the contrast relevant to synaesthetic colour processing (inducing letters black > non-inducing symbols black (lb>sb)), and for exploratory analysis of veridical colour processing (coloured Mondrians > greyscale Mondrians (cMond>gMond)). Psychological variables were the experimental time points of the condition block weighted by each contrast and convolved with a canonical HRF. The interaction variable was constructed from the psychological variable, multiplied by the deconvolved physiological variable.

4.3.5 First and second level designs

Image preprocessing was conducted as described in Section 3.3.6. Briefly, preprocessing consisted of slice timing correction, spatial realignment of EPI images to the mean EPI image, co-registration of the structural and mean EPI images followed by normalisation to the SPM8 MNI T1 template. Mean image normalisation parameters were then applied to the remaining EPI images, and all EPI images were smoothed with an 8 x 8 x 8 mm FWHM Gaussian kernel, and bandpass filtered with a 128 Hz cut off to remove low frequency signal drifts.

First level designs were constructed with SPM5, with estimation and contrasts conducted using SPM8. Models contained the physiological, psychological and interaction variables, along with the 6 rigid body movement parameters created from realignment of the EPI images. First level contrasts were weighted on the interaction variable, with the physiological, psychological and motion variables included as regressors of no interest, to remove and variance associated with main effects of the seed region activity, the experimental condition or participant movement.

Second level designs were constructed from the first level contrast images using SPM8. Second level random effects analysis was completed separately for synaesthetes and controls for each of the seeds and contrasts tested. Second level two-sample designs were constructed for synaesthetes > controls and controls > synaesthetes in the exploratory analysis. A second level covariate regression was also constructed on the random effects results of synaesthetes for each seed and contrast, using scores for localisation (CLaN-L), with attention and automaticity (CLaN-A) additionally tested in the exploratory analysis. Second level designs were initially thresholded liberally at $k = 10$ and $p(uncorrected) < .005$. Corrections were applied to assess the specific hypothesis of connectivity between parietal, colour areas and letter shape regions, as van Leeuwen, den Ouden, and Hagoort (2010). To assess connectivity between parietal and colour areas, a small volume correction was applied to the parietal seed functional connectivity map using a masked area defined by the main effect of veridical colour (coloured Mondrian > greyscale Mondrian) used for the functional localisation of colour areas. The mask was built from the collapsed second level results from both groups in the main effect of veridical colour. The masked area includes regions of left and right V1, V2, V4, V5 and ventral V3 (as labelled by the SPM CYTO anatomy toolbox), and is functionally defined as an area which is selectively responsive to colour at the group level. To assess connectivity between individually localised colour areas, a small volume correction was applied to FC maps generated by individually defined colour areas using a search volume generated by a masked area of the left and right inferior parietal clusters identified in the interaction between group and synaesthetic induction (synaesthetes[lb>sb] > controls[lb>sb]) described in the Chapter 3. For the assessment of connectivity between parietal or colour areas and a LSA, a masked area of the left fusiform gyrus was used in a small volume correction of the relevant functional connectivity maps, as van Leeuwen, den Ouden, and Hagoort (2010). Significant results are reported as those surviving family-wise correction at the peak or cluster level at $p(FWE) < .05$. Significant peaks and clusters were labelled using the AAL toolbox

(Tzourio-Mazoyer et al., 2002) for SPM8.

4.4 Results

PPI analysis was conducted on the fMRI data of synaesthetes and controls in order to identify brain areas which show modulation of functional connectivity by experimental condition and activity in a seed region. The 'seed' represents a ROI identified in the GLM analysis of the same data, as described in Table 4.1, and relates to individually defined colour selective areas and parietal regions defined in the interaction between group and synaesthetic induction. A 'target' represents a brain area in which the BOLD response is influenced by the interaction between the seed activity and the experimental condition, such that this region responds to the experimental condition when and only when activity in the seed region is high. The results of the between groups comparison demonstrate areas of functional connectivity which are significantly different between the groups. The analysis of individual differences demonstrates how phenomenological variability in the localisation (CLaN-L) or automaticity (CLaN-A) of concurrents influences seed and target coupling. The results of the PPI analysis are presented in Tables 4.3 and 4.2. The results presented here are obtained through analysis of the data acquired in Chapter 3. The results of Chapters 3 and 4 are therefore not independent, and the results presented here should be interpreted as an extension of the analysis presented in Chapter 3.

4.4.1 Synaesthetic colour processing

The PPI assessment of functional connectivity during synaesthetic colour processing (letters coloured black (lb) > symbols coloured black (sb)) shows that parietal seeds identified in interaction between group and synaesthetic induction have no significant coupling with any other areas of the brain at the group level, and this coupling is not modulated by individual differences in CLaN-L. To assess the specific hypothesis of functional connectivity between parietal and colour areas, a small volume correction was applied on parietal seed connectivity using a masked area of the group level veridical colour response; this small volume correction showed no significant differences between synaesthetes and controls in functional connectivity between parietal and colour areas, at the group level. Small volume corrections also showed no significant differences between synaesthetes and controls in functional connectivity between parietal areas and the left fusiform gyrus (LSA). Parietal FC with small volume corrections to colour areas or the FG were not modulated by individual differences in CLaN-L.

Colour areas show no significant differences in coupling between synaesthetes and controls across the whole brain. Small volume corrections also showed no significant difference

Table 4.2: Group differences in PPI connectivity results in synaesthetic colour processing (inducing letters coloured black (lb) > non-inducing symbols coloured black (sb)). There were no significant differences in effective connectivity for controls > synaesthetes.

Seed	Target	Cluster p(FWE)	Cluster k	Peak p(FWE)	Peak Z	x	y	z
		Synaesthetes: CLaN-L						
Right colour areas	Cuneus and lingual gyrus	<.001	968	.984	3.747	8	-80	0

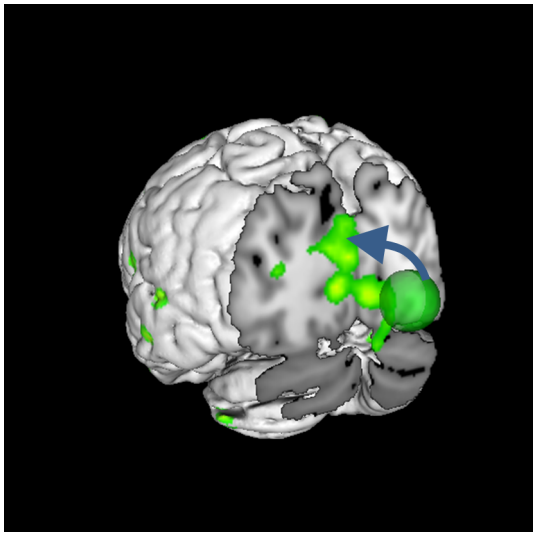


Figure 4.1: Individual differences in coupling in synaesthetes based on localisation of concurrents (CLaN_L) with influence from right colour selective areas in synaesthetes (represented by spherical ROI centred on the mean co-ordinates of synaesthetes right colour sensitive area [24, -81, -3] with radius 1 sd of those co-ordinates (14.6 mm) to right lingual gyrus [8, -80, 0] $p(FWEcluster) < .001, k = 968, p(FWEpeak) = .984, Z = 3.747$.

between synaesthetes and controls, in FC seeded from individually defined colour areas and to the two parietal clusters or the left fusiform gyrus (LSA). Individual colour area FC was, however, modulated by individual differences in CLaN-L, with increased localisation of concurrents associated with increased coupling between right colour areas and the cuneus, with a peak in the lingual gyrus ($p(FWEcluster) =< .001, k = 968, p(FWEpeak) = .984$, $p(Unc.peak) < .001, Z = 3.747$) (see Figure 4.1).

4.4.2 Veridical colour processing

Exploratory PPI assessment of functional connectivity in veridical colour processing shows synaesthetes to have increased coupling between the OperRIFG and the left calcarine

Table 4.3: Group differences in PPI connectivity results in contrasts veridical colour processing (coloured Mondrians > greyscale Mondrians).

Seed	Target	Cluster p(FWE)	Cluster k	Peak p(FWE)	Peak Z	x	y	z
		Controls > Synaesthetes						
Left colour areas	Inferior frontal gyrus orbital (R)	.000	715	.244	4.450	44	28	-4
	Anterior cingulum (L)	.036	332	.918	3.821	-4	36	18
	Superior temporal pole (L)	.032	340	.995	3.575	-48	10	-12
		Synaesthetes > Controls						
OperRIFG	Calcarine sulcus (L)	.009	495	.859	3.849	-14	-66	6
		Synaesthetes: CLaN-A						
Right colour areas	Paracentral lobule (L)	.026	355	.753	4.077	-10	-22	76

sulcus during veridical colour processing (see Figure 4.2).

In synaesthetes alone, random effects analysis of the OperRIFG seed shows a significant cluster of activation in the left anterior precuneus ([-2, -60, 16], $p(FWEcluster) = .004, k = 470, p(FWEpeak) = .361, p(Unc.peak) < .001, Z = 4.416$) which overlaps with the left calcarine sulcus cluster from the same seed in the group differences of synaesthetes > controls (see Figure 4.3). This suggests that there is an increase in coupling between the OperRIFG, the anterior precuneus and medial superior parietal lobe during veridical colour processing for synaesthetes compared to controls. Synaesthetes also show individual differences in coupling during veridical colour processing, dependant on the automaticity of their concurrents (CLaN-A).

Controls were found to have significantly increased coupling compared to synaesthetes between left colour selective areas and i) orbital part of the right inferior frontal gyrus, and (ii) the left anterior cingulate, and iii) the left superior temporal gyrus (see Figure 4.4 and Table 4.3). This coupling is not significant in the assessment of controls as a group (i.e. in random effects analysis) and only significant in comparison to synaesthetes. This suggests that this coupling is not a feature of normal veridical colour processing, rather that synaesthetes show significantly reduced coupling compared to controls in these areas.

Figure 4.2: Increased coupling in synaesthetes compared to controls during veridical colour processing between (A) the OperRIFG seed (spherical 8 mm radius ROI [48, 12, 12]) and (B) the left calcarine sulcus [-14, -66, 6] $p(FWEcluster) = .009, k = 495, p(FWEpeak) = .859, Z = 3.849$.

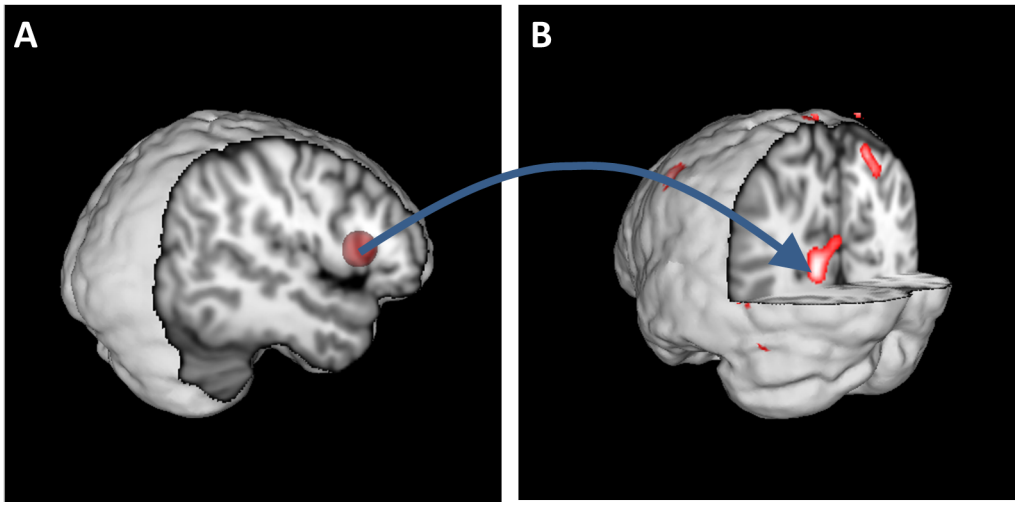


Figure 4.3: Overlap in medial superior parietal lobe targets (circled in first slice) during veridical colour processing (coloured Mondrians > greyscale Mondrians). Identified in (red) group differences (synaesthetes > controls) in coupling from the OperRIFG seed, and (green) random effects analysis of synaesthetes in coupling from the OperRIFG seed.

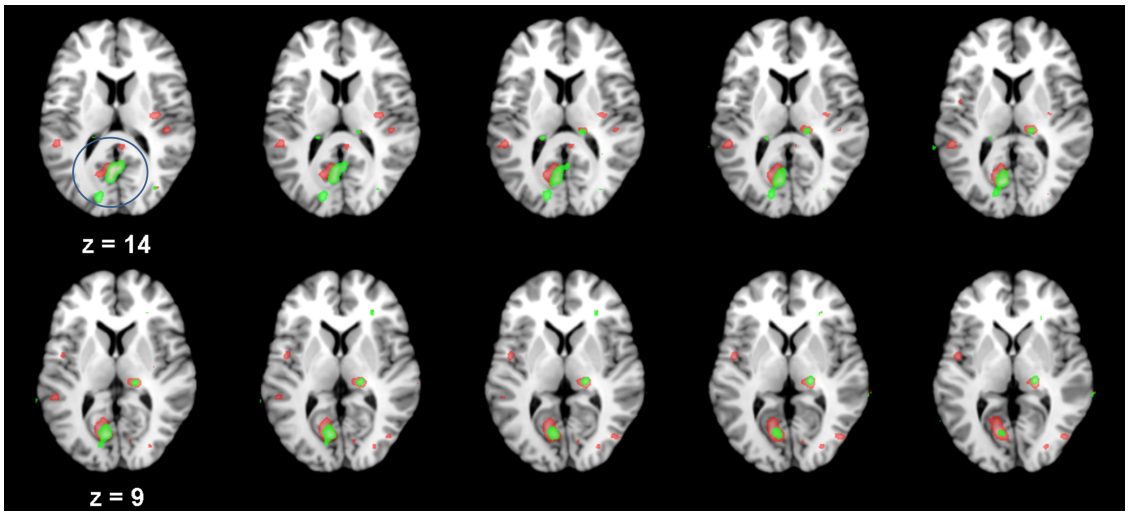
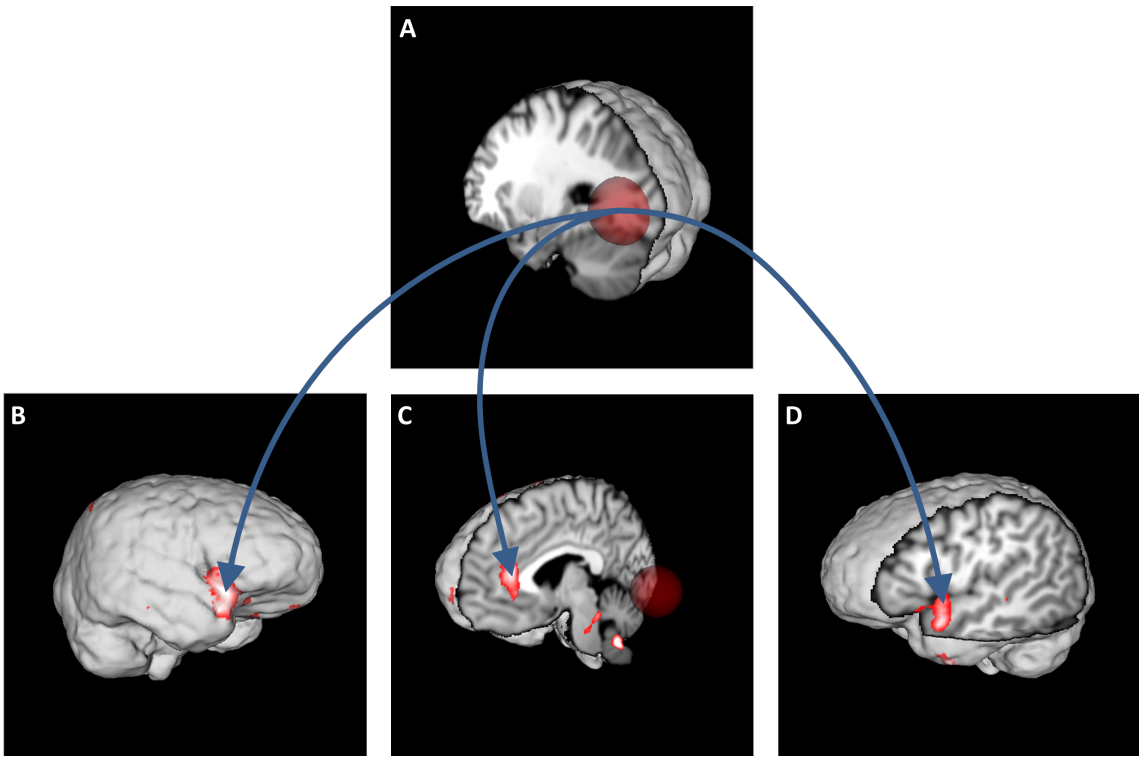


Figure 4.4: Increased coupling in controls compared to synaesthetes in veridical colour processing. Coupling between (A) left hemisphere colour selective areas and (B) right frontal gyrus [44, 28, -4] $p(FWEcluster) < .001, k = 715, p(FWEpeak) = .244, Z = 4.450$, (C) left anterior cingulate [-4, 36, 18] $p(FWEcluster) = .036, k = 332$, $p(FWEpeak) = .918, Z = 3.821$ and (D) left superior temporal gyrus [-48, 10, -12] $p(FWEcluster) = .032, k = 340, p(FWEpeak) = .995, Z = 3.575$. The seed area (A) is represented by a spherical ROI centred on the mean co-ordinates of the left colour selective areas in controls [-25, -72, -3] with radius 1 sd of those co-ordinates (18.3 mm).



4.5 Discussion

We assessed group differences in functional connectivity of synaesthetes and controls using the PPI method, to determine whether the effective connectivity model of van Leeuwen et al. (2011) reflected trait differences relevant to synaesthesia, that is, whether the functional co-activation of colour, letter and parietal areas under synaesthetic conditions differs between synaesthetes and controls. As per van Leeuwen et al. (2011), we investigated the impact of synaesthetic phenomenology on this network, under the hypothesis that the projector-associator differences reported by van Leeuwen et al. (2011) would be similarly identifiable through regression against individual differences in CLAN-L scores. Unlike van Leeuwen, den Ouden, and Hagoort (2010); van Leeuwen et al. (2011), we found no evidence for a significant difference between synaesthetes and controls in functional connectivity between colour and parietal areas, even after small volume correction. Parietal-colour connectivity was not modulated by individual differences in CLaN-L, nor was functional connectivity between the fusiform gyrus (where van Leeuwen, den Ouden, and Hagoort (2010) report their letter shape area to be located) and colour areas. These data suggest that the effective connectivity model proposed by van Leeuwen et al. (2011) is not trait specific to synaesthesia, as it was not identifiable at FWE corrected threshold in this cohort relative to controls. The data also suggest that the strength of this network is not modulated by individual differences in phenomenology, as measured on a continuous localisation score. Together, these data suggest that the classically proposed "bottom-up" letter-colour-parietal network, and "top-down" letter-parietal-colour network may not be a significant contributor to the synaesthetic experience.

4.5.1 Synaesthetic colour processing

In synaesthetic colour processing, our data show that of the areas hypothesised to play a significant role in functional connectivity of synaesthesia (namely letter, colour and parietal), none were found to have a significantly increased functional connectivity in synaesthetes relative to controls, to any part of the brain nor the prespecified letter, colour and parietal areas. We do, however, find functional connectivity between right hemisphere individual colour selective areas and a large cluster in the cuneus to be modulated by individual differences in localisation of concurrent. It appears then that our functional connectivity analysis does not support the effective connectivity model of van Leeuwen et al. (2011), there are a number experimental differences which may account for this discrepancy, and there are underlying similarities.

In returning to the original functional connectivity analysis of van Leeuwen, den Ouden, and Hagoort (2010), we note that they only report FC between SPL and colour areas, and state explicitly that FC between colour areas and the LSA was not apparent in their population, even at low, uncorrected thresholds. It may not then be surprising that we identified no significant FC between the FG and colour areas in our population. It is more surprising however that we were unable to detect FC between colour and parietal areas in our population, even after small volume correction. This difference perhaps speaks to the group differences between in the synaesthetes test in these investigations; although we attempted to control for individual differences in synaesthetic phenomenology by conducting regression analysis, it is possible that the predictive power of our model was limited by the range of experiences of our cohort. A large proportion of the participants in the studies of van Leeuwen, den Ouden, and Hagoort (2010); van Leeuwen et al. (2011) where classified as projectors, whereas the present cohort contained only 2 projectors by their definition. Although the CLaN-L data were normally distributed, there was a (non-significant) positive skew, with a larger proportion of the participants reporting low localisation of concurrents. It is possible that the inclusion of synaesthetes with a greater degree of localisation would have influenced the model such that the colour-parietal FC was detectable through regression against individual differences. There also remains a key difference in the method of selection of the colour area seeds: whilst both investigations functionally localised colour areas, the V4 component of the van Leeuwen et al. (2011) model was identified through a contrast of black inducing graphemes > black non-inducing graphemes, whereas individual colour areas were defined here with an independent functional localised contrasting coloured Mondrians > greyscale Mondrians. This difference was necessary as we found no evidence for colour area activity in the inducers versus non-inducers condition for our cohort (as discussed in Chapter 3), however we did find that activity in functionally defined colour areas to be modulated by CLaN-L, so it was hypothesised that FC seeded from these areas would also be modulated by CLaN-L.

The results of the present investigation supports a bottom up theory of concurrent induction, as evidenced by our FC between right hemisphere individual colour areas and a large cluster in the cuneus. This connectivity was found to be modulated by CLaN-L such that greater the localisation of concurrents predicts FC between colour areas and low level visual areas. The target of the right colour area seed was found to encompass areas of V1, V2 and the optic radiation (as labelled by the SPM CYTO toolbox), but

primarily covers the cuneus. This suggests that the greater highly localised concurrents, which we assume to be the experience of high scouring projectors, are associated with strong connectivity with colour and early visual processing areas. This is aligned with the model of van Leeuwen et al. (2011) in that projectors feature increased bottom up connectivity compared to controls, however in this case we find the cuneus to relate to the colour area activity and not the letter shape area. This interpretation also lends support to the suggestion that synaesthesia arises from a hyper-sensitivity of the colour processing stream, as evidenced by a hyper-excitability of early visual areas (Terhune et al., 2011). Further investigations are required in order to more fully understand the role of the cuneus and early visual areas in the synaesthetic experience, perhaps through the development of effective connectivity models which encompass the cuneus in their models.

4.5.2 Veridical colour processing

In our exploratory analysis of functional connectivity in veridical colour processing, synaesthetes have a generally reduced network of areas compared to controls which is functionally connected to left hemisphere colour area activation. Specifically, synaesthetes had significantly less functional connectivity between left colour areas and i) orbital part of the right inferior frontal cortex, ii) the left superior temporal pole, and iii) the left anterior cingulate. Reduced coupling between left colour areas in veridical colour processing of synaesthetes suggests that either they do not engage in the same feed-forward processing as controls, or they do not experience feed-back modulation of colour stimulus information. The reduced functional connectivity between left colour areas and the rest of the brain may account in part for the trend for increased activity in right hemisphere colour areas in synaesthetes in veridical colour processing (see Chapter 3).

Synaesthetes shows increased coupling compared to controls between the OperRIFG and the left calcarine sulcus during veridical colour processing. We previously suggested that OperRIFG activity in veridical colour processing suggested that synaesthetes respond to veridical colour as an 'important' or salient stimulus. Increased activity in calcarine sulcus when OperRIFG activity is high suggests that the processing of colour as a salient stimulus may be coupled with an increased perceived brightness of the colour stimulus, as V1 activity has been found to correlate with perceived stimuli brightness (Haynes, Lotto, & Rees, 2004; Rossi, Rittenhouse, & Paradiso, 1996). We therefore hypothesise that the influence of OperRIFG activation serves to boost the response of the primary visual response to colour stimuli for synaesthetes, via feedback modulation. This boost of the V1

response may account in part for the trend for increased colour area activation observed in synaesthetes compared to controls in response to veridical. A simple behavioural experiment could be used to assess differences in perceived brightness of veridical colour between synaesthetes and controls. For example, a two forced-choice luminance discrimination task could be employed (e.g. as Odgaard, Arieh, and Marks (2003)), in which synaesthetic and control participants are presented with coloured and achromatic stimuli. In a proportion of the trials, the stimuli could consist of objectively variant luminance (control trials) to determine the levels of detection in objective luminance variance, whilst in experimental trials the achromatic and coloured stimuli could be objectively matched in luminance. Support for our suggestion that synaesthetes show increased perceived brightness of colour stimuli would be found in their rating of coloured stimuli as brighter than luminance matched achromatic stimuli.

The target of effective connectivity with the OperRIFG seed was shown to peak in the anterior precuneus when synaesthetes were assessed as a group, an area shown to be involved in self-relevant information processing (Cavanna & Trimble, 2006; Kircher et al., 2000; Vogeley et al., 2001). This FC may also be trait relevant if synaesthetes determine colour stimuli to be 'self-relevant'. DCM may be usefully applied to determine the precise nature of the relationship between the OperRIFG, precuneus and V1 responses.

In summary, synaesthetes show less network engagement than controls of left hemisphere colour areas during veridical colour processing, but increased coupling between the OperRIFG, primary visual areas and areas related to self-relevant information processing. We speculate that the reduced engagement of left colour areas contributes to the trend for increased responsiveness of synaesthetes relative to controls in right colour area activity as described in Chapter 3. We also suggest that the coupling between the OperRIFG and V1 may lead to an increase in perceptual brightness of coloured stimuli for synaesthetes, with the 'salience' of colour stimuli relating both to OperRIFG and precuneus activity. We describe a simple behavioural paradigm which could be used to test this prediction.

4.6 Conclusions

We investigated functional connectivity in GCS and controls to assess whether the functional and effective connectivity model proposed by van Leeuwen, den Ouden, and Hagoort (2010) and van Leeuwen et al. (2011) was trait specific to synaesthesia and whether it was modulated by individual differences in localisation of concurrents. Unlike van Leeuwen, den Ouden, and Hagoort (2010), we did not find evidence for functional connectivity at

group level for synaesthetes between parietal and colour areas. There was no significant difference in this connectivity between groups, and this was not modulated by individual differences in synaesthetic phenomenology. We did, however, find evidence for bottom-up functional connectivity to be modulated by individual differences in localisation, with greater connectivity between colour and early visual areas with increasing localisation of concurrents. This is tentative support for the bottom-up network being more relevant to projectors compared to associators, as suggested by van Leeuwen et al. (2011), however there was no evidence in the present data that this bottom-up connectivity involved areas relevant to letter processing directly. Our data also lend support to the suggestion of Terhune et al. (2011) that GCS is accompanied by differences in early visual processing compared to controls. We propose that further investigations of FC and EC on GCS encompass a wider region of areas in model specification, with particular regard to the inclusion of early visual areas.

Chapter 5

Resting state functional connectivity in grapheme-colour synaesthetes

5.1 Chapter summary

Functional connectivity in resting state fMRI (rsFC) refers to temporal correlations in spontaneous fluctuations across disparate brain areas. These functional networks are present in the absence of external stimulation, and are therefore termed as intrinsic connectivity networks (ICNs), and are assume to be supported by structural connectivity. Investigations of rsFC in grapheme-colour synaesthesia (GCS) have previously demonstrated alterations in FC between synaesthetes and controls across all networks relevant to synaesthesia, including visual, auditory and parietal networks Dovern et al. (2012).

In this Chapter we present rsFC analysis of GCS participants ($n = 20$) and matched controls ($n = 20$). We use the robust independent component analysis (ICA) method in an attempt to replicate the FC results of Dovern et al. (2012). In an extension, we investigate the impact of individual differences in synaesthesia phenomenology upon ICNs. Based on the results of individual differences investigations in functional activation (Chapter 3) and context specific FC (Chapter 4), it was hypothesised that localisation of concurrents (CLaN-L) would modulate the rsFC of visual networks. Exploratory analysis was also conducted on the impact of automaticity of concurrents (CLaN-A).

In between groups analysis, we replicate Dovern et al. (2012) in increased rsFC in the right front-parietal network in synaesthetes compared to controls. We note however that the precise location of increased rsFC in our cohort is in the left middle occipital gyrus, whereas Dovern et al. (2012) reported increased rsFC in middle and superior frontal areas. However, we fail to replicate Dovern et al. (2012) in the identification of increased rsFC in synaesthetes compared to controls in the lateral visual network (LVN), auditory network (AN), left fronto-parietal network (LFPN) or lateral parietal network (LPN). This discrepancy in findings may be due to methodological differences in rs-fMRI data collection, or they may be due to individual differences in the two synaesthetic populations investigated.

In accordance with our hypothesis, individual differences in concurrent localisation were found to modulate rsFC in the LVN. Specifically, localisation of concurrents was found to significantly predict coupling between the cuneus and LVN as a whole, such that increased coupling between the cuneus and the LVN was associated with increased localisation of concurrents. This area of the cuneus was also identified in the analysis of individual differences in CLaN-L on context specific FC (Chapter 4)), suggesting that the intrinsic connectivity of lower visual areas may be modulated by localisation, determining both rsFC and context specific effects. This demonstration provides support for the cross

wiring theories of GCS, but suggest that this direct connectivity may be between lower and higher visual areas, and not between grapheme and colour areas directly. Exploratory analysis of individual differences in CLaN-A found rsFC in medial parietal network (MPN), LFPN and RFPN all to be modulated by CLaN-L. This suggests that whilst localisation of concurrents impacts visual ICNs, automaticity of concurrents is related to activities in parietal ICNs. The far reaching impact of individual differences in phenomenology on ICNs may account in part for the discrepancies in findings between Dovern et al. (2012) and the present investigation, however, no phenomenological information is provided by zDovern et al. (2012), so we are unable to verify the claim. This emphasises the importance of detailed description and investigation of experiential phenomenology in neural investigations.

5.2 Introduction

We have demonstrated that both experimental BOLD activation (Chapter 3) and context specific functional connectivity (FC) are modulated by individual differences in synaesthetic phenomenology. In this Chapter, we investigate resting state FC (rsFC) to determine the impact of individual differences in synaesthetic phenomenology on neural connectivity in the absence of any external stimulation.

5.2.1 Resting state functional connectivity

During 'resting state' fMRI (rs-fMRI) data collection, participants are not actively engaged in an experimental task, thus correlations in the temporal signature across different brain areas arise spontaneously rather than being evoked by an external stimulus. Spontaneous activity in the brain is responsible for the vast majority of neuronal metabolic demand; over 80% of glucose metabolism can be attributed to spontaneous activity during resting states (Raichle & Mintun, 2006).

Resting state networks are reflected in slow fluctuations in BOLD signal (<0.1 Hz) and show temporal correlations across functionally related brain areas (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox & Raichle, 2007). Resting state networks can be shaped by anatomical networks (Damoiseaux & Greicius, 2009; Honey, Kötter, Breakspear, & Sporns, 2007) and can therefore be considered intrinsic to the brains structure and function. It has been suggested that the low frequency signals of these intrinsic connectivity networks (ICNs) represent slow cortical potentials related to cortical excitability (Schroeder & Lakatos, 2009), with demonstrated effects on stimulus-related evoked responses and behavioural performance (see Raichle (2010) for a review). A number of different ICNs have been identified, each including a specific collection of brain areas. The precise purpose of each ICN is still to be determined, although they are assumed to each support different functional roles. In the most limited view, ICNs can be considered to represent areas which interact with each other. Regions which are simultaneously engaged in task-positive activity have been shown to maintain synchrony in task-negative resting states (e.g. Biswal et al. (1995)) and may be supported by structural connectivity (Damoiseaux & Greicius, 2009). The composition of each ICNs is not fixed and may be modulated by experimental demands prior to rs-fMRI data collection (see e.g. Stevens, Buckner, and Schacter (2010)), and have been shown to differ in clinical populations. Relating the regional deviation to known functions of an area may help explain some of the symptomatology of clinical patients. In schizophrenia for example, the default mode network (DMN) has been shown to

be over-active and have altered connectivity with other ICNs (Buckner, Andrews-Hanna, & Schacter, 2008). The DMN is involved in mind wandering and self-referential activity (Gusnard, Akbudak, Shulman, & Raichle, 2001), thus over-activity of the DMN may account for the positive effects of schizophrenic symptomatology such as disturbances of thought and hallucinations.

A number of methods have been developed to investigate ICNs in rs-fMRI, including ROI/seed based analysis, independent component analysis (ICA), graph methods, clustering algorithms and multivariate pattern classification (see Lee, Smyser, and Shimony (2012) for a review of rs-fMRI analysis methods). ROI based rsFC analysis was the first method developed (Biswal et al., 1995) and is used to assess temporal correlations between the seed area and all other voxels in the brain. This approach is hypothesis driven as it relies on the initial selection of a relevant ROI for other activity to be correlated with. ICA by distinction is more data-driven than ROI analysis. The ICA method decomposes low frequency resting state fluctuations in BOLD signal into a number of independent components, based the temporal signature of each voxel and how they correlate with all other voxels in the brain over the course of the resting state data collection. These components therefore reflect areas of the brain which are temporally related and thereby form a single functional network in the absence of external stimulation. ICA decomposition is based on the assumption that source signals for each network are independent; a given number of maximally independent source signals are identified, highlighting a number of ICNs which are orthogonal to every other network identified. In fMRI, these ICNs are transformed into spatial maps which indicate the degree of correlation of each voxel with the source signal of the relevant network. This method has been shown to consistently produce a number of specific networks during resting state, across varied sample populations (Damoiseaux et al., 2006). The ICNs identified by ICA typically include:

1. **Default mode network (DMN)**: Precuneus/posterior cingulate, lateral parietal cortex and medial prefrontal cortex;

2. **Sensory motor network (SMN)**: Precentral gyrus, postcentral gyrus and supplementary motor area;

3. **Medial visual network (MVN)**: Medial striate cortex and medial extra-striate regions such as the lingual gyrus;

4. **Lateral visual network (LVN)**: Lateral visual areas such as the occipital pole and occipito-temporal regions;

5. **Striate and polar visual network (SPVN)**: Striate and polar visual areas;

6. **Executive control network (ECN)**: Medial frontal gyrus, superior frontal gyrus, anterior cingulate cortex;

7. **Left and right lateralised fronto-parietal network (L/RFPN)**: Inferior frontal gyrus, medial frontal gyrus, precuneus, inferior parietal lobe, angular gyrus;

8. **Auditory network (AN)**: Superior temporal gyrus, Heschl's gyrus, insula, post-central gyrus;

9. **Temporo-parietal network (TPN)**: Inferior frontal gyrus, medial temporal gyrus, superior temporal gyrus, angular gyrus. (Adapted from Rosazza and Minati (2011))

Whereas ICA analysis is data driven and exploratory, graph theoretic methods of analysis are hypothesis driven. Graph methods assess ICNs in relation to 'nodes' of interest. The nodes are assessed for characteristics such as the length between nodes, average connection length and the shortest length between nodes. These descriptions have been used to characterise the brain as displaying small world topology, where each node is connected to every other via a low number of short connections and intermediary hubs (van den Heuvel, Stam, Boersma, & Hulshoff Pol, 2008). ROI and ICA based analysis have been shown to produce similar results in control populations (Rosazza, Minati, Ghielmetti, Mandelli, & Bruzzone, 2012), but no such comparisons have been made for graph theoretic networks.

5.2.2 rsFC in grapheme-colour synaesthesia

Resting state FC of synaesthetic populations has been investigated by combined ICA and ROI methods (Dovern et al., 2012) and graph theoretic analysis (Tomson, Narayan, Allen, & Eagleman, 2013). In Dovern et al. (2012) the ICNs of 12 grapheme-colour synaesthetes and 12 matched controls were assessed, using data collected on a 3T MRI system. ICA was used for model free exploration of the rs-fMRI data and complemented with seed based correlation analysis using an anatomically defined V4 ROI. Data from both synaesthetes and controls were collapsed to generate a robust set of ICNs, of which a subset of seven were selected to be of relevance to synaesthetic networks. These specific networks included visual, auditory or intraparietal cortices and were deemed relevant as these areas had been identified across a number of fMRI studies of synaesthesia (Hubbard & Ramachandran, 2005; Nunn et al., 2002; Rouw & Scholte, 2007, 2010; Weiss & Fink, 2009; Weiss et al.,

2005). Within these seven ICNs, a number of areas showed statistical differences in FC between synaesthetes and controls. Synaesthetes had small clusters which showed significantly increased coupling with the network source signal compared to controls across LVN, AN, LFPN, RFPN, MPN and LPN. The majority of these clusters of increased connectivity fall inside the regions typically ascribed to each ICN. For example, synaesthetes were found to have significantly greater coupling between the right superior and right middle frontal gyrus with the source signal of the RFPN. This suggests that the RFPN has a similar functional role in synaesthetes and controls, as the same functional areas are engaged in each, but the network as a whole is integrated more heavily with these frontal areas. In the LVN, increased functional connectivity was observed outside the spatial distribution normally expected for that network; synaesthetes were found to have increased coupling between the right lingual gyrus and the LVN source signal compared to controls. This suggests that the normal functional role of the LVN in processing visual information draws more heavily on lingual gyrus related functions in synaesthetes.

In the present investigation we sought to replicate the rsFC results of Dovern et al. (2012), using the ICA methods which have previously been shown to reproducibly characterise ICNs across different populations. In an extension of the Dovern et al. (2012) investigation, we present data from a larger sample population and investigate the impact of individual differences in synaesthetic phenomenology on rsFC networks. It was hypothesised that the results of the between groups comparison of synaesthetes and matched controls would be consistent with the investigation of Dovern et al. (2012), if these effects were group level traits. Specifically, it was hypothesised that synaesthetes would show increased functional connectivity within all synaesthesia relevant networks, as Dovern et al. (2012). This hypothesis was assessed using a between groups comparison of each independent rsFC network, in the direction of synaesthetes $>$ controls, and controls $>$ synaesthetes, as Dovern et al. (2012).

As the Chapters 3 and 4 clearly demonstrated the individual differences in phenomenology can impact the neural data across a number of regions, it was hypothesised that inconsistencies between the results of the present investigation and that of Dovern et al. (2012), may be the result of variation in the phenomenological experience of the two synaesthetic cohorts. In Chapter 4 it was demonstrated that localisation of concurrents (CLaN-L) predicted the degree of FC between right hemisphere colour selective areas and the cuneus. As regions which are simultaneously engaged in task-positive activity have been shown to maintain synchrony in task-negative resting states, it was hypothesised that this CLaN-

L mediated FC in visual areas would be similarly identified in rsFC. Specifically, it was hypothesised that individual differences in localisation of concurrents would modulate the rsFC of visual networks, as the PPI investigation of Chapter 4 found coupling between right colour areas and the cuneus to be modulated by CLaN-L, with both the seed and target areas of this coupling within visual cortices. This hypothesis was assessed through regression of whole-brain visual network maps against individual CLaN-L scores, with a positive result suggested significant positive correlation between CLaN-L and visual network rsFC. We note that context specific differences in FC was also found in assessment of veridical colour processing, with controls showing significantly greater coupling between colour areas and frontal, cingulate and superior temporal regions. Synaesthetes showed significantly increased coupling between the OperRIFG and calcarine sulcus in veridical colour processing, along with modulation of coupling between right colour areas and the precentral lobe by CLaN-A. As these results were obtained in exploratory analyses, they were not taken forward in the formation of hypotheses for rsFC in the present Chapter. We also note that the placement of rs-fMRI data collection following extended synaesthetic induction served to maximise group differences resulting from the synaesthetic experience. Accordingly, it was hypothesised that the group and individual difference FC effects in veridical colour processing would be minimally detected in rsFC.

5.3 Methods

We assessed rsFC networks in synaesthetes and controls and determine how ICNs are modulated by individual differences in synaesthetic phenomenology. We aimed to replicate the ICA results of Dovern et al. (2012) by following the same methods and extended this analysis by conducting regression against individual differences in the first-person synaesthetic experience.

5.3.1 Participants

The conduct of this research was approved by the Research Governance and Ethics Committee for Brighton and Sussex Medical School (Project Approval Reference: 10/049/GOU). Participants were 20 grapheme-colour synaesthetes and 20 age, gender, handedness and education level matched controls, as described in the previous Chapters (Section 3.3.1). All participants took part in pre-screening for MRI safety, reported no history of physiological or psychological trauma and had normal colour vision. Control participants reported no synaesthesia of any form for themselves or 1st and 2nd degree relatives. Synaesthesia was confirmed through completion of the online synaesthesia battery (Eagleman et al., 2007) with all synaesthetes falling within the range of acceptable scores in consistency in concurrent colour selection (see Section 3.4.1.3). Synaesthetes additionally completed the CLaN synaesthesia phenomenology questionnaire (Rothen, Tsakanikos, et al., 2013), being scored on their localisation (CLaN-L) and automaticity (CLaN-A) of concurrents, as described in Section 3.3.3 and Section 3.4.1.

5.3.2 Imaging

Data were acquired at the Brighton and Sussex Medical School Sussex Clinical Imaging Sciences Centre using a Siemens Avanto 1.5T system. A T1 weighted structural image was acquired (TR 1160 ms, TE 4.44 ms, flip angle 15°, voxel size 0.9 x 0.9 x 0.9 mm, 192 slices, 0.45 mm slice gap) followed by an echo-planar imaging (EPI) sequence for functional volumes (TR 2210 ms, TE 30 ms, flip angle 90°, voxel size 3 x 3 x 3 mm, 36 slices, 0.75 mm slice gap). 212 functional volumes were acquired over 7 minutes 49 seconds. Data were acquired following 615 s of visual stimulation with blocks of coloured and achromatic graphemic inducers and non-inducers (data presented in Chapters 3 and 4). Data were acquired following synaesthetic induction in this was in order to maximally activate the synaesthesia relevant networks and maximise group differences. During rs-fMRI, participants were instructed to rest with their eyes closed but remain alert.

5.3.3 Image analysis

The first 5 rs-fMRI volumes for each subject were discarded to allow for magnetisation stabilisation. The remaining volumes were preprocessed before independent component analysis (ICA). Preprocessing consisted of slice timing correction followed by motion correction through realignment of all EPI images using a six parameter rigid body transformation to a mean EPI image. The mean image was then co-registered with the structural and normalised to the SPM8 MNI T1 template. The mean image normalisation parameters were then applied to the remaining EPI images and all EPI volumes were smoothed with an 8 x 8 x 8 mm FWHM Gaussian kernel. Images were filtered with a phase-insensitive band-pass filter (0.01 - 0.08 Hz) to reduce the effects of low frequency drift and high frequency physiological noise (Koch et al., 2012).

ICA was conducted using the Group ICA for fMRI toolbox (GIFT) (Calhoun, Eichele, Egolf, & Rachakonda, 2013). ICA was used to decompose fMRI signal into spatially segregated regions with common low frequency fluctuations. Following Dovern et al. (2012), GIFT was used to identify 25 independent components using the FastICA algorithm (Hyvärinen, 1999). Full details of FastICA using GIFT have been published elsewhere (e.g. Correa, Adali, and Calhoun (2007)). At the group level, analysis followed 1) data reduction to 25 components; 2) application of the FastICA algorithm; 3) back reconstruction of the spatial components for each subject. Individual IC maps were converted to Z-scores for second level parametric statistical analysis to render functional connectivity independent of the original BOLD signal magnitude.

Data from both synaesthetes and controls were collapsed to generate a robust set of ICNs relevant for all participants, as Dovern et al. (2012). Previous studies have shown that visually identified component selection produces similar results to spatial template matching (Franco, Pritchard, Calhoun, & Mayer, 2009), therefore the 25 independent components from the collapsed data set were inspected visually to identify those corresponding to components of no interest (e.g. white matter, cerebrospinal fluid or artefacts). Among the remaining components, ten spatial patterns were identified corresponding to known ICNs (Damoiseaux et al., 2006; Rosazza & Minati, 2011) and a further pattern corresponding to the medial parietal network (MPN) of Dovern et al. (2012). Synaesthesia relevant ICNs were identified as those involving visual, auditory and parietal areas, as Dovern et al. (2012). Z-maps for each participant therefore represent the degree of correlation of each voxel with the temporal signature of the source signal of the network. ICA was also conducted separately on each group with identical parameters as the collapsed group ICA,

to validate the presence of all synaesthesia relevant ICNs in both groups, as Dovern et al. (2012).

Between group analysis was conducted on each of the synaesthesia networks to detect within-network differences in rsFC, that is, significant differences between groups in the degree of correlation of temporal signature of each voxel with source signal. This second level analysis was achieved via a two-sample t-test, using the reconstructed z-maps for each participant and comparing them group-wise between synaesthetes and controls. Contrasts were constructed in the direction of synaesthetes $>$ controls, and controls $>$ synaesthetes, as Dovern et al. (2012). This analysis was used to test the hypothesis that group differences in rsFC would be detected within each of the synaesthesia relevant resting state networks, as reported in Dovern et al. (2012).

To investigate the impact of individual differences on rsFC networks, a simple regression analysis was conducted for each component against individual CLaN-L scores. Each synaesthesia relevant ICN was modelled separately and comprised of individual z-maps for that ICN, with an individual CLaN-L scores entered as a co-variate. The model was then weighted positively on the CLaN-L co-variate, to find regions of rsFC within the network which were predicted by the CLaN-L score. As our hypothesis related to increased FC with increased localisation, all regressions were weighted positively. The same method was applied in exploratory analysis of the impact of individual differences in CLaN-A scores.

5.4 Results

We investigated FC in synaesthetes compared to controls to determine whether the differences in rsFC reported by Dovern et al. (2012) were trait level and consistent with the rsFC networks identified in the present cohort. We also investigated the impact of individual differences in synaesthesia phenomenology on rsFC, to test the hypothesis that rsFC in the LVN is modulated by concurrent localisation. Data were collapsed across groups in order to identify robust ICNs and analysed using ICA into 25 separate components. Components relating to physiological noise or imaging artefacts were disregarded (14 components) leaving those relating to temporal correlations between distinct cortical regions (ICNs).

Eleven ICNs were identified in data collapsed across both groups (Figure 5.1 (see Appendix C Tables C.1 to C.3 for a complete list of areas within each network). Of these network, group differences in rsFC were assess in all visual, auditory and parietal networks identified. This included the MVN, LVN, striate and polar visual network (SPVN), AN, temporo-parietal network (TPN), MPN, LFPN and RFPN. All synaesthesia relevant ICNs were identified in the ICA conducted on both groups separately, however, in synaesthetes alone two separate MVNs and LFPNs were identified (see Figure 5.5).

In the collapsed group networks, differences were found between groups and within synaesthetes based on individual differences in localisation and automaticity of concurrents (see Table 5.1). In group differences, synaesthetes were found to have increased coupling between the left middle occipital gyrus and the RFPN source signal (see Figure 5.2). There were no statistically significant differences in synaesthetes compared to and controls in the MVN, LVN, AN, TPN, MPN, of LFPN. There were no significantly greater areas of FC in controls compared to synaesthetes.

In individual differences, localisation of concurrents modulated rsFC within the LVN (see Figure 5.3). Specifically, CLaN-L predicted coupling of the cuneus with the LVN source signal, such that increased coupling was predicted by increased CLAN-L score. CLaN-L also positively predicted coupling of the left parahippocampal area. In exploratory analysis of the impact of automaticity, CLaN-A was found to influence functional connectivity in the SMN, the MPN, the LFPN and RFPN (see Figure 5.4) with increased in regional coupling to the network source signal in the right middle temporal gyrus, right middle frontal gyrus and cerebellum respectively.

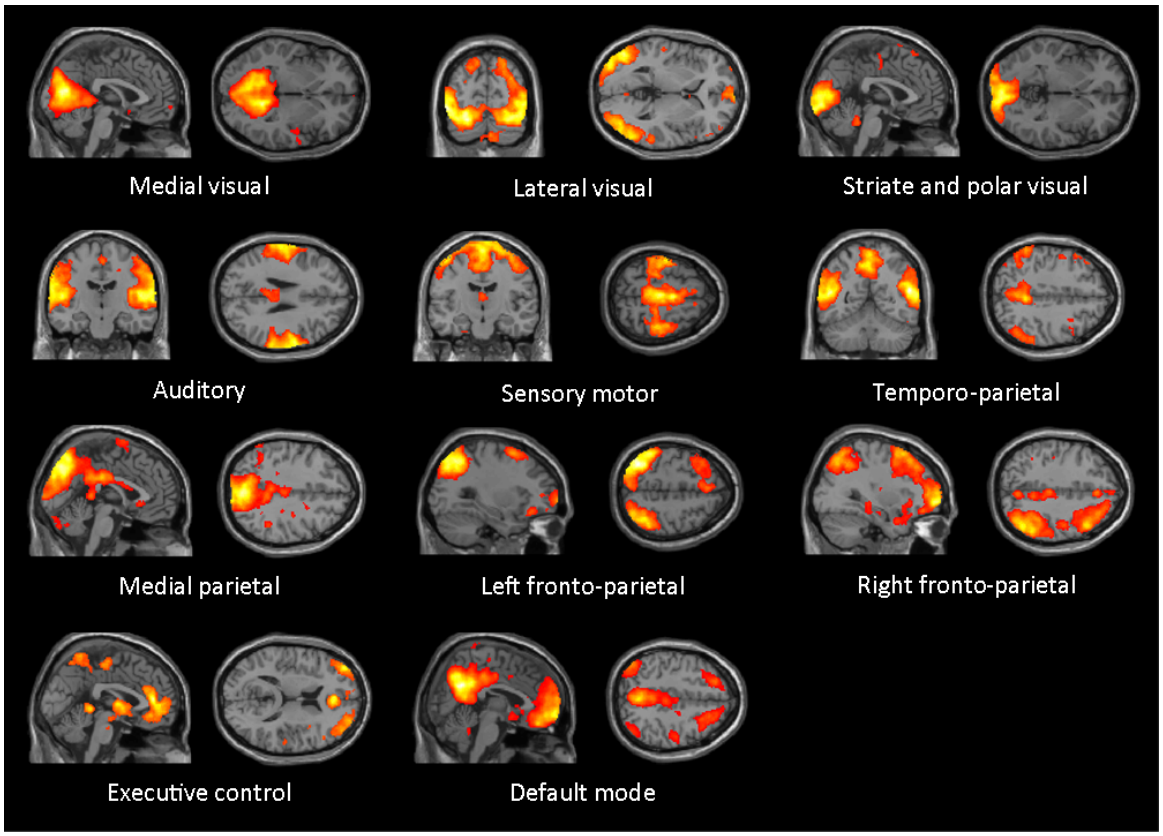


Figure 5.1: rs-fMRI ICNs identified by ICA, collapsed across synaesthetes and controls. Collapsed data show the characteristic profile of rs-fMRI ICNs as consistently identified in control populations (Damoiseaux et al., 2006), along with the medial parietal network identified in both synaesthetes and controls by Dovern et al. (2012). Threshold $p(Unc.peak) < .001$. Colour scale (red-white) = t score 0-10.

Table 5.1: Group and individual differences in rsFC within ICNs. 2nd level maps thresholded at $p(Unc.peak) < .001, k = 10$. Significant peaks and clusters reported at $p(FWE) < .005$.

Network	Area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Peak Z	x	y	z
		Synaesthetes > Controls						
Right Fronto-parietal	Middle Occipital (L)	.827	86	.013	5.283	-54	-76	18
		Synaesthetes: CLaN-L						
Lateral visual	Cuneus (R)	.203	144	.033	5.124	6	-88	34
	Parahippocampal (L)	.037	213	.971	3.983	-18	-24	-14
		Synaesthetes: CLaN-A						
Medial parietal	Middle Temporal (R)	.020	240	.100	3.710	56	-40	-2
Left fronto-parietal	Middle Frontal (R)	.049	210	.357	4.582	36	-6	52
Right fronto-parietal	Cerebellar Crus2 (L)	.021	241	.965	3.996	-10	-78	-30

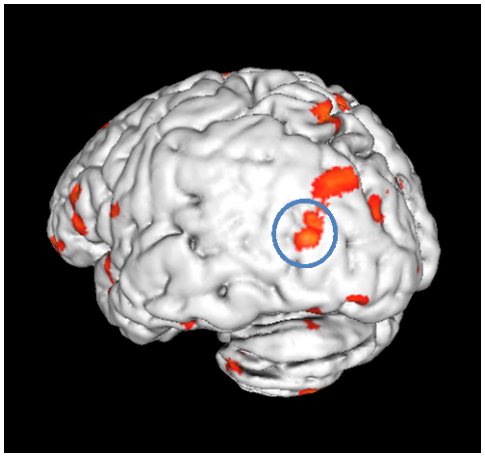


Figure 5.2: Significantly increased coupling between the left middle occipital gyrus and the source signal of the RFPN in synaesthetes compared to controls $[-54, -76, 18], p(FWEcluster) = .827, k = 86, p(FWEpeak) = .013, Z = 5.283$.

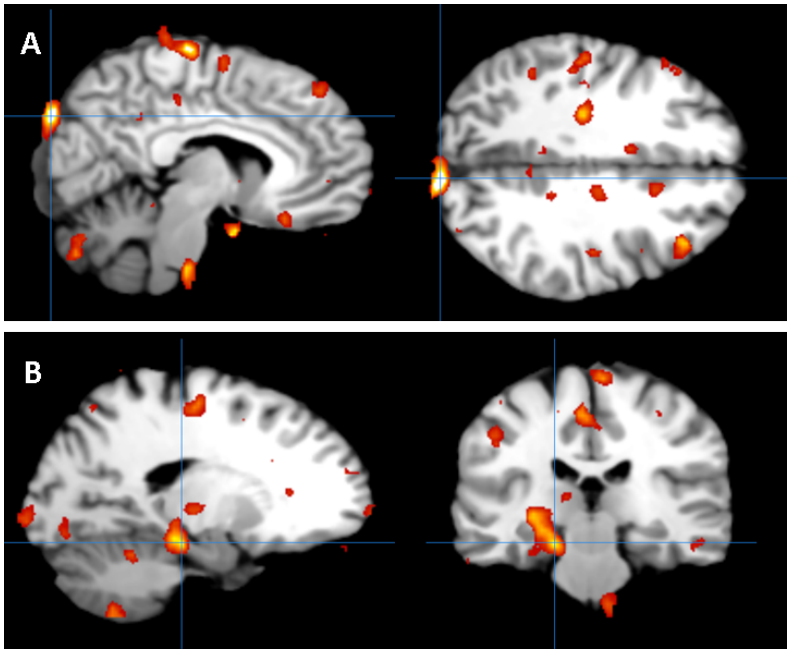


Figure 5.3: Positive correlation between CLaN-L and FC in the LVN in (A) the right cuneus ($[6, -88, 34], p(FWEcluster) = .203, k = 144, p(FWEpeak) = .033, Z = 5.124$) and (B) the left parahippocampal gyrus ($[-18, -24, -14], p(FWEcluster) = .037, k = 213, p(FWEpeak) = .971, Z = 3.983$).

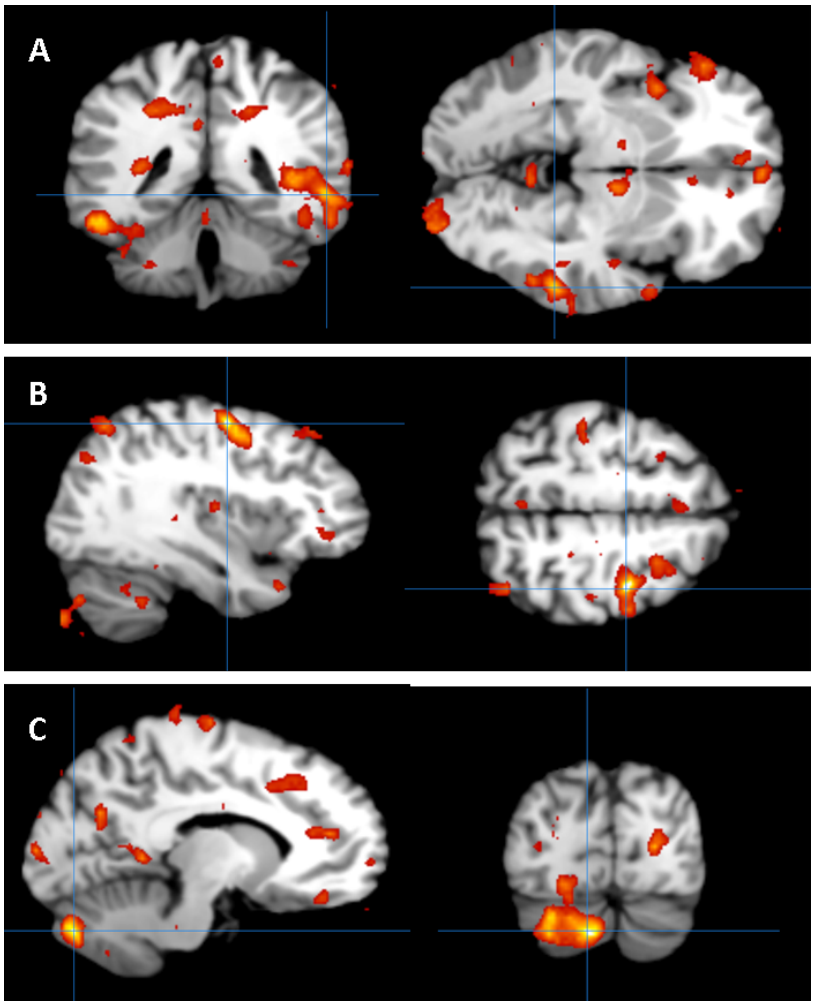


Figure 5.4: Positive correlation between CLaN-AA and significant coupling of a region with the source signal of that network. Identified in, (A) the right middle temporal lobe coupling with the MPN [56, -40, -2] ($p(FWEcluster) = .020, k = 240, p(FWEpeak) = .100, Z = 3.710$); (B) the right middle frontal lobe and the LFPN [36,-6, 52]($p(FWEcluster) = .049, k = 210, p(FWEpeak) = .357, Z = 4.582$); (C) the left cerebellar crus II and the RFPN in the ($[-10, -78, -30], p(FWEcluster) = .021, k = 241, p(FWEpeak) = .965, Z = 3.996$).

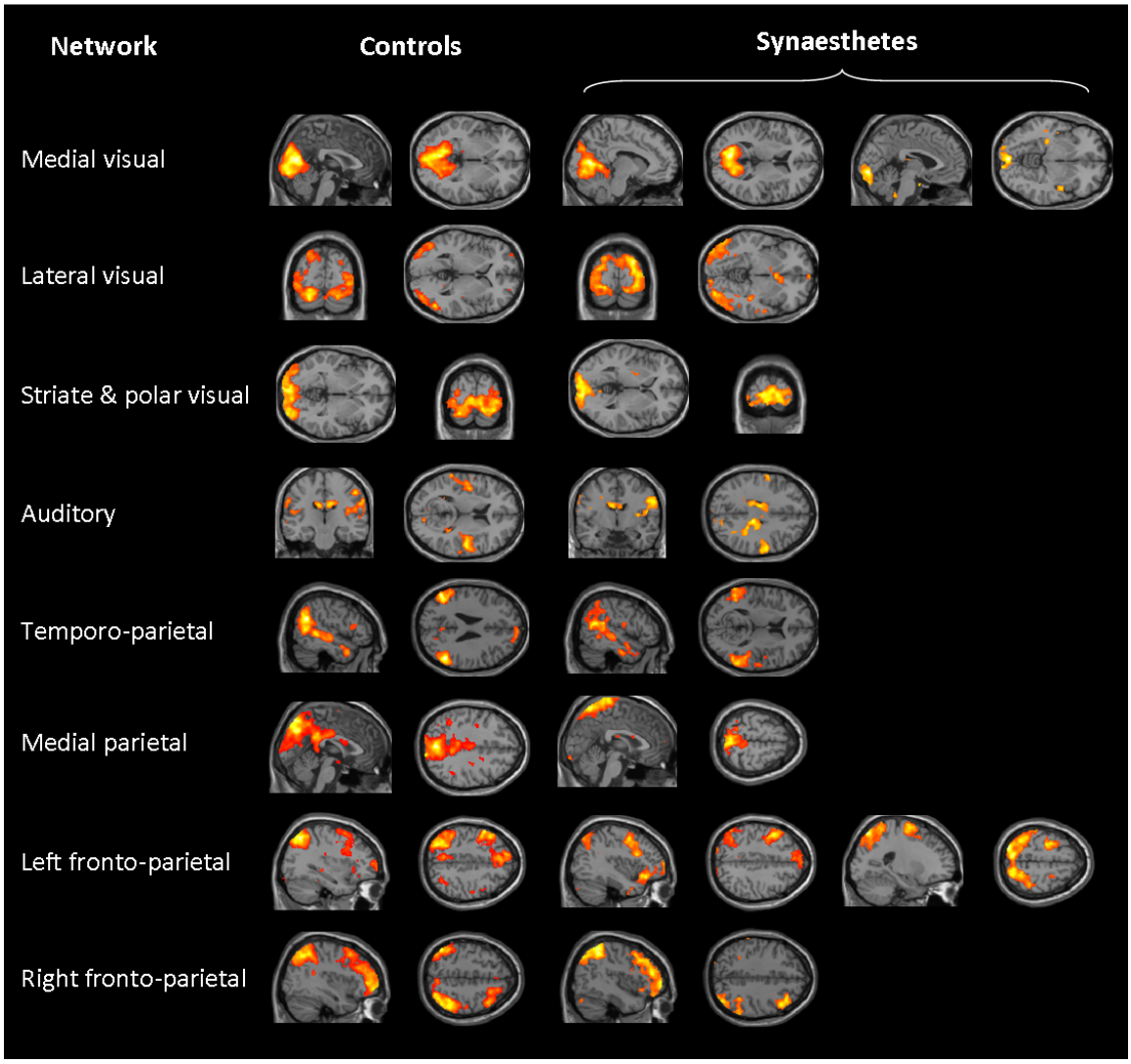


Figure 5.5: ICNs identified following ICA analysis of rs-fMRI in separate groups of synaesthetes and controls. Threshold $p(Unc.peak) < .001$. Colour scale (red-white) = t score 0-10.

5.5 Discussion

We present an investigation of ICNs in GCS through assessment of rsFC of grapheme-colour synaesthetes and matched controls. We sought to replicate and extend the rsFC results of Dovern et al. (2012) using the same ICA methodology, but with and additional assessment of the impact of individual differences in synaesthesia phenomenology, specifically localisation of concurrents (CLaN-L) and exploratory analysis regarding the impact of automaticity of concurrents (CLaN-A). It was hypothesised that the results of the between groups comparison would be consistent with Dovern et al. (2012) if these effects were group level traits. Specifically, it was hypothesised that synaesthetes would show increased functional connectivity compared to controls within visual, auditory and parietal networks, whilst controls would show increased rsFC within the LFPN and RFPN, as Dovern et al. (2012). We failed to replicate the wide ranging differences in rsFC reported by Dovern et al. (2012), as we found no significant group differences in the MVN, LVN, AN, TPN, MPN, of LFPN. Consistency between the present investigation and that of Dovern et al. (2012) was, however, observed in significant differences in that RFPN, with synaesthetes showing increased coupling between the left middle occipital gyrus and the RFPN source signal. This consistency importantly suggests that the RFPN may then be considered a significant network in the generation of aspects of synaesthetic phenomenology, behavioural and fMRI response patterns which are common to all GCS participants.

In the case of individual differences, it was hypothesised that localisation of concurrents would predict a modulation of coupling within visual networks, as context specific FC (Chapter 4) showed coupling between colour areas and the cuneus to be predicated by CLaN-L. The data presented here support this hypothesis by demonstrating modulation of LVN by localisation of concurrents, but additionally show a significant positive relationship between parahippocampal coupling with the LVN source signal. In exploratory analysis regarding the impact of CLaN-A, automaticity of concurrents was predictive of differences across all parietal networks. Through this assessment of individual differences, we are able to detect effects across all networks identified in the between groups analysis of Dovern et al. (2012), except in auditory network. This suggests that individual differences in phenomenology have a large impact on intrinsic connectivity patterns in synaesthetes, with localisation of concurrents modulating visual networks, whilst automaticity of concurrents modulates parietal networks. This finding may be relevant in further exploration of localisation and automaticity effects, through the generation of hypotheses which relate to visual and parietal network activities respectively.

5.5.1 Group differences in rsFC

In the between groups comparison, there was a significant increase in rsFC in synaesthetes compared to controls in the RFPN only, with increased coupling between the left middle occipital gyrus and the RFPN source signal. No further group differences were identified in rsFC in the MVN, LVN, AN, TPN, MPN or LFPN RFPN. There were no significantly greater areas of FC in controls compared to synaesthetes across any synaesthesia relevant networks. This suggests that trait level differences in rsFC are only present in the RFPN, as this is the only network in which group differences were detected by both the present investigation and that of Dovern et al. (2012). In the present investigation the specific area of difference within the RFPN was localised to the posterior region of the left middle occipital gyrus, with this area showing a significant increase in coupling with the RFPN. This suggests that the normal function of the RFPN additionally recruits this posterior region of the occipital lobe in synaesthetes compared to controls in our population. The main components of the RFPN include the inferior frontal gyrus, medial frontal gyrus, precuneus, inferior parietal lobe and angular gyrus. These regions have been implicated in a wide range of cognitive functions, including memory (Damoiseaux et al., 2006), language (Smith et al., 2009), attention (Dosenbach et al., 2007; Fox et al., 2005) and visual processes (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006) and thus it is difficult to ascribe a single role to the network. RFPN, along with LFPN are, however, particularly susceptible to modulation by prior sensory-motor learning, and it has been suggested that they play a role in memory consolidation Albert, Robertson, and Miall (2009). This suggests that for our cohort, this memory consolidation process involved visual areas to a greater extent for synaesthetes compared to controls. The investigation of Dovern et al. (2012) found increased coupling in synaesthetes compared to controls between the RFPN source signal and clusters in the right middle frontal gyrus and right superior frontal gyrus. The discrepancy in the precise regional localisation of differences in the RFPN may be related to experimental differences in data acquisition (for example, our data were collected on a 1.5T system, whereas the data for Dovern et al. (2012) were collected on a 3T system), but equally they may result from individual differences in synaesthetic phenomenology of the cohorts investigated (see Section 5.5.2 below).

A further methodological difference between the present investigation and that of Dovern et al. (2012) relates to our positioning of the data collection following a sustained period of synaesthetic induction, in order to maximise the group differences in rsFC. When analysed separately, synaesthetes were found to have an increase in the number of indi-

vidual synaesthesia relevant ICNs identified, with an additional MVN and LFPN (see Figure 5.5). As discussed above, the LFPN and RFPN have been shown to be modulated by experience immediately prior to rs-fMRI data collection. The same effect has been observed in visual networks, such that task related activity can be subsequently detected in rsFC networks (Stevens et al., 2010). Our design has enabled the detection of alterations in rsFC which can be identified as two separate and independent time signatures from the same group of functionally related structures. Of particular note is the similarity between the LFPN networks identified when ICA was conducted on synaesthetes alone, and the results of the interaction between group and synaesthetic induction reported in Chapter 3 (see Figure 5.6). This 'splitting' of LFPN may suggest that the LFPN is engaged in two separate functions in the resting state, only one of which is a function also implicated in resting state activity of controls. The LFPN identified in controls alone has a composition closely resembling the LFPN of the collapsed data, both of which include a diffuse set of areas including the angular gyrus, cerebellum, frontal, parietal and temporal cortices. By distinction, the two LFPN networks of synaesthetes alone are more discrete, with one involving primarily frontal cortices and no parietal regions, whilst the other involves frontal, parietal and temporal regions. Where the LFPN has a putative role in memory consolidation, the statistical independences of the two synaesthete LFPNs might suggest two separate memory consolidation processes, one of which we suggest relates uniquely to the synaesthetic experience. Similarly, a medial visual network limited to the calcarine fissure was identified in both groups, which relates to functions of the early visual cortex during resting state. However, the additional MVN network was identified in synaesthetes, with coupling between primary visual areas and frontal, hippocampal, parietal and temporal regions. This suggest a functional integration between activity of primary visual areas with a further distributed network for synaesthetes and not controls. As this network we not identified in controls, we propose that this integration of visual activity with a wider distributed network is uniquely relevant to the synaesthetic experience.

5.5.2 Individual differences in rsFC

Individual differences in ICNs were assessed thorough regression of whole brain rsFC maps against CLaN-L and CLaN-A. As predicted, localisation of concurrents modulated rsFC of visual networks, with increasing CLaN-L predicting increased coupling of the cuneus with the LVN source signal. This supports our hypothesis that both intrinsic rsFC and context specific FC of the cuneus with visual areas is impacted by localisation of

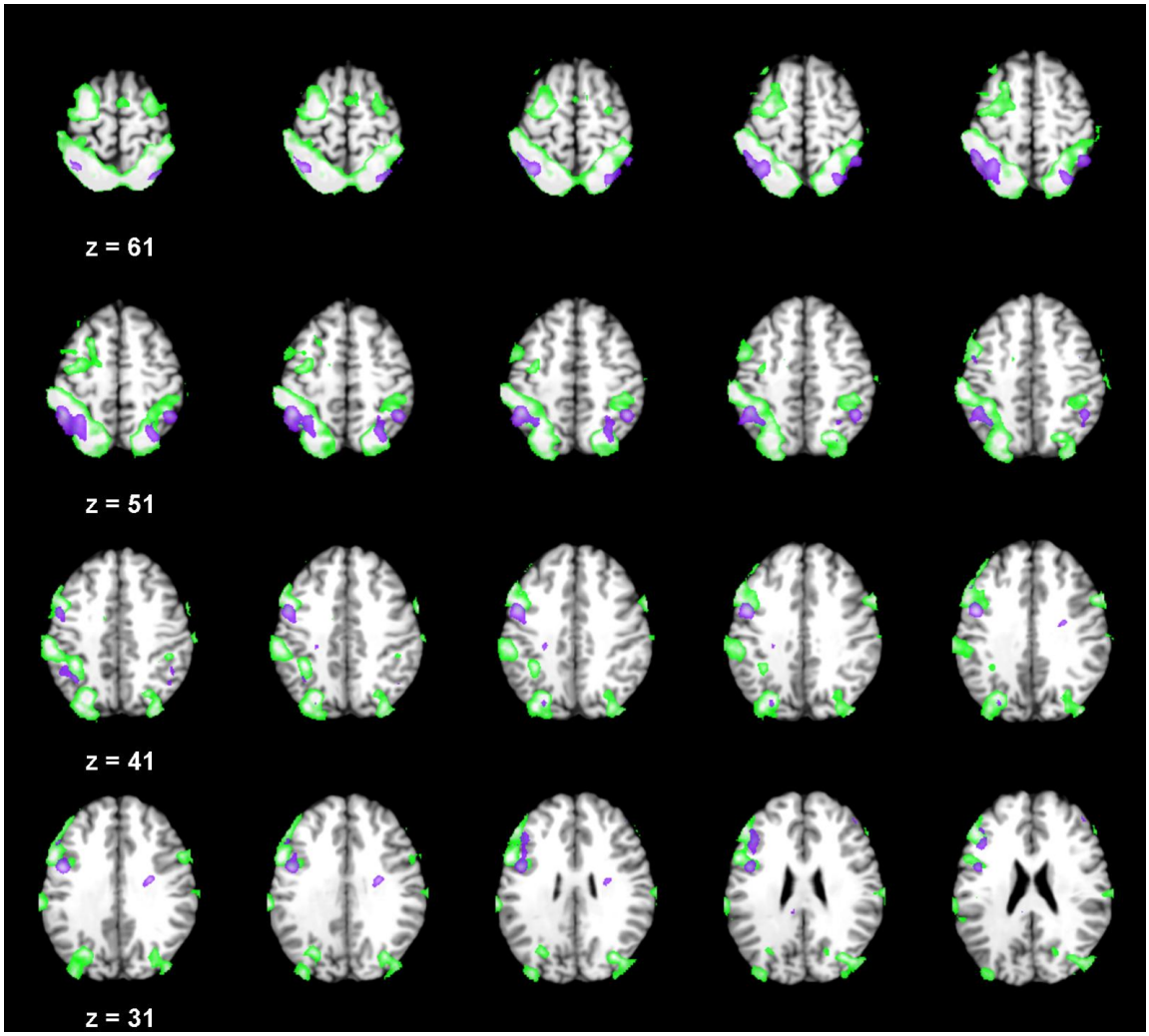


Figure 5.6: Overlap between the additional LFPN identified in rsFC of synaesthetes (green) and the group differences (synaesthetes > controls) in functional activation in synaesthetic colour processing (black inducers > black non-inducers) (purple).

concurrents. This suggests that increased localisation of concurrents draws on low level visual processes, supporting the bottom-up theory of concurrent generation. Unlike the classic bottom-up model of synaesthesia, however, these results implicate activity in the cuneus in concurrent generation, rather than the visual word form area. As with Chapter 4, this finding supports the hyper-excitability model of Terhune et al. (2011), which proposes synaesthesia to arise from and increased sensitivity in the concurrent processing stream, arising through increased sensitivity of low level visual areas in synaesthetes compared to controls.

We additionally found CLaN-L to predict coupling of the parahippocampal gyrus with the LVN source signal. It is possible that the increased FC in parahippocampal areas predicted by increased CLaN-L is responsible in part for the highly precise and localised nature of the experience, whereas reduced parahippocampal FC may lead to a more abstract (unlocalised) concurrent experience. Parahippocampal FC was reported by Rouw and Scholte (2010) to be a feature of associator synaesthetes to a greater extent than projector synaesthetes. Whilst high scores in CLaN-L may be more closely correlated with projector synaesthetes, the relationship between associators and CLaN-L is more difficult to resolve, therefore the finding of engagement of parahippocampal areas in the LVN and its relationship to an internalised associator-type experience will require further investigation.

Our exploratory analysis regarding automaticity of concurrents was found to be predictive of differences across parietal networks, specifically the MPN, LFPN and RFPN. The description of automaticity in concurrents relates to the amount of directed attention required in order for the synaesthete to become aware of their concurrent experience. High automaticity suggests that the concurrent is a salient feature of the synaesthetes experience. This exploratory analysis therefore suggests that the 'breakthrough' of the synaesthetic experience is related to the functional properties of integrated parietal networks.

We have demonstrated individual differences to have a significant impact on the composition of rsFC networks. Given the impact of individual differences, the variation in phenomenological experience between the present cohort and that of Dovern et al. (2012) may also be a significant contributor to the failed replication of the group effects reported in Dovern et al. (2012). The only phenomenological descriptions of the cohort investigated by Dovern et al. (2012) relate to 'consistency' in synaesthetic experience, as calculated by a comparison between the written descriptions of 129 colour concurrents over a minimum

6 months test-retest period. This crude measure of phenomenology was found to predict the correlations between ICNs, however, a more precise descriptor (e.g. Eagleman (Eagleman et al., 2007), or CIELUV (Rothen, Seth, et al., 2013) consistency scores) may be beneficial. We suggest, however, that the use of validated first-person descriptors such as the CLaN factors of localisation and automaticity may be particularly beneficial in aiding our understanding of the trait as a whole, through inference from the phenomenological experience to the neural activity.

5.6 Conclusions

The RFPN consistently shows differences in rsFC between groups of synaesthetes and matched controls. This suggests trait level variation in the role of the RFPN in synaesthetes compared to controls, potentially relating to variations in memory consolidation processes during resting state conditions. This consistency importantly suggests that the RFPN may be a considered significant network in the generation of aspects of synaesthetic phenomenology, behavioural and fMRI response patterns which are common to all GCS participants. As there is little consistency between the regional localisation of areas of increased coupling within the RFPN between the present investigation and that of Dovern et al. (2012), further investigation will be required to determine how this trait variation is most frequently manifested. The present investigation, however, suggests that memory consolidation in synaesthetes is more heavily coupled with the functions of the left middle occipital gyrus.

In accordance with our hypothesis, individual differences in CLaN-L were found to positively predict the degree of coupling between the cuneus and the LVN. This supports our finding of increased context specific FC between right hemisphere colour areas and the cuneus (Chapter 4), and the suggestion that increased localisation is supported by increased connectivity with low level visual processing. We additionally demonstrate in exploratory analysis that CLaN-A modulates parietal ICNs. This relationship suggests parietal targets in further investigations of the neural determinants of automaticity in synaesthetic concurrents. These investigations highlight the requirement for complete and accurate descriptions of phenomenology in the investigation of the synaesthetic experience.

Chapter 6

Summary and conclusions

6.1 Summary

Synaesthesia is a cognitive trait in which stimuli of one sensory modality are automatically and consistently experienced in conjunction with perceptions in a separate modality or processing stream. The trigger for these percepts is known as the inducer and the synaesthetic perception is known as the concurrent. Examples include auditory-colour synaesthesia, in which specific combinations of colour and motion are perceived in response to auditory stimuli (Cytowic, 1989) and lexical-gustatory synaesthesia, in which the auditory or visual presentation of words is associated with sensations of tastes (Ferrari, 1907; Pierce, 1907). Synaesthetes do not experience their synaesthetic percepts in a manner akin to associating the smell of cut grass with a Summer's day, rather evidence to date suggests that synaesthetic concurrents may exist to varying degrees in the external perceptual world. The study of synaesthesia is of particular relevance to the study of consciousness as synaesthetes have a conscious experience (concurrent) which is not directly attributable to an external stimulus, that is to say, although an inducing item (e.g. a letter) is present in the external environment, the concurrent percept (e.g. a colour) is not. This means that the conscious concurrent experience must be indirectly generated. Any investigations which can shed light on the processes involved in concurrent generation may thereby open a window into the generation of other conscious experiences, be they indirectly generated or otherwise. Synaesthesia also provides a unique opportunity to study altered conscious states in a population which are on the whole free from significant clinical disorders; as synaesthetes are otherwise healthy we may expect any differences in neural or behavioural data to be free from some of the more complex interactions which may be found in clinical psychiatric disorders of consciousness.

In order to gain the most complete understanding of synaesthesia, it is necessary to approach investigations from a number of complementary methodological viewpoints. In this thesis we have presented first person qualitative analysis along with quantitative investigations with fMRI. Throughout we have placed emphasis on the effect of individual differences and demonstrated that synaesthetes of any kind should not be viewed as a single homogeneous group. We have shown that the qualitative experience of the participant can affect functional activation, context specific FC and resting state FC in a way which can aid the interpretation of our data and guide future investigations. In the qualitative first person investigation (Chapter 2) we have shown that aspects of the spatial form synaesthesia experience can be usefully explored to a far greater extent than is currently practised. Through guided introspection in the Elicitation Interview method, we identify

features of the concurrent experience were previously unknown even to the subject, including a tendency for inner speech following visual inducer presentation. Where SFS would normally be described as a visual-to-visual experience for this subject, our analysis demonstrates that it also involves an auditory-to-visual mechanism. Our results suggest that it will be possible to gain similar in-depth phenomenological descriptions of other aspects of synaesthesia phenomenology, bringing benefit to behavioural and neuropsychological investigations, not only of SFS but also other forms.

In quantitative fMRI analysis (Chapters 3-5), we present a comprehensive and multi-analytic investigation of synaesthetic colour processing. In all cases, we demonstrate differences between a large group of synaesthetes ($n = 20$) and controls ($n = 20$), along with differences within the group of synaesthetes based on two newly developed phenomenological measures of localisation and automaticity in concurrents (Rothen, Tsakanikos, et al., 2013). These measures are distinct from previously applied projector-associator dimensions by their continuous nature, providing inherent statistical advantages over existing dichotomous measures.

In Chapter 3 we investigate functional activation in GCS and demonstrate that the degree of activation in colour areas during the synaesthetic experience is predicted by individual differences in localisation and automaticity of concurrents, implying that previous failed attempts to replicate the key finding of colour area activation at the group level may have been the result of variation in individual phenomenology along these dimensions. These results resolve an outstanding debate in the synaesthesia literature (activation of colour-specific areas in GCS) by combining fMRI with individual differences in phenomenology, exemplifying the approach of 'neurophenomenology' (Varela, 1996).

In Chapter 4 we investigated context specific functional connectivity in GCS and controls using a psychophysical interaction (PPI) analysis, to assess whether the connectivity model proposed by van Leeuwen, den Ouden, and Hagoort (2010); van Leeuwen et al. (2011) in which projectors featured bottom-up connectivity from letter areas, to colour areas, with both inputs being subsequently integrated in the SPL. Associators, by distinction, were reported by van Leeuwen et al. (2011) to feature top-down connectivity, with letter areas coupled with the SPL, and subsequent activation of colour areas. We specifically aimed to assess whether SPL and colour area connectivity during synaesthetic induction conditions was trait specific, through comparison of FC networks in synaesthetes compared to controls. We additionally assessed the proposed projector and associator differences, through regression against the phenomenological measures of

localisation (CLaN-L) and automaticity (CLaN-A). It was predicted that the similarity between CLaN-L and projector-like experiences would enable the detection of FC between colour and letter areas in regression against CLaN-L, such that increased localisation would predict increased coupling between a region in the left fusiform gyrus and colour areas, in accordance with the bottom-up model. In testing these hypotheses, we found no evidence for functional connectivity at group level for synaesthetes between parietal and colour areas. There was no significant difference in this connectivity between groups, and this was not modulated by individual differences in synaesthetic phenomenology. We did, however, find evidence for bottom-up functional connectivity to be modulated by individual differences in localisation, with greater connectivity between colour and early visual areas predicted by increasing localisation of concurrents. This is tentative support for the bottom-up network being more relevant to projectors compared to associators, as suggested by van Leeuwen et al. (2011), however there was no evidence in the present data that this bottom-up connectivity involved areas relevant to letter processing directly. Our data lend support to the suggestion of Terhune et al. (2011) that GCS is accompanied by differences in early visual processing compared to controls, leading to a hyper-excitability of the colour processing stream. We propose that further investigations of FC and EC on GCS encompass a wider region of areas in model specification, with particular regard to the inclusion of early visual areas. We also report exploratory analysis of veridical colour processing, and find increased functional connectivity in synaesthetes compared to controls between the OperRIFG and early visual areas. We propose that this coupling may contribute to an increased in perceived brightness of colour stimuli for synaesthetes, accounting in part for the relative importance of colour stimuli for this population.

In Chapter 5 we demonstrate that rsFC is not only altered in synaesthetes as compared to controls, but that the specific intrinsic connectivity networks (ICNs) are modulated by individual differences. We show that the recruitment of areas into the RFPN is consistently altered between synaesthetes and controls, as this network is altered in both the rsFC investigation of Dovern et al. (2012) and in the present synaesthetic cohort. This suggests trait level variation in the role of the RFPN in synaesthetes compared to controls, potentially relating to variations in memory consolidation processes during resting state conditions. This consistency importantly suggests that the RFPN may be a considered significant network in the generation of aspects of synaesthetic phenomenology, behavioural and fMRI response patterns, common to all GCS participants. As there is little consistency between the regional localisation of areas of increased coupling within

the RFPN between the present investigation and that of Dovern et al. (2012), further investigation will be required to determine how this trait variation is most frequently manifested. The present investigation, however, suggests that memory consolidation in synaesthetes is more heavily coupled with the functions of the left middle occipital gyrus.

As hypothesised, individual differences in CLaN-L were found to positively predict the degree of rsFC coupling between the cuneus and the LVN. This supports our finding of increased context specific FC between right hemisphere colour areas and the cuneus (Chapter 4), and the suggestion that increased localisation is supported by increased connectivity with low level visual processing. We additionally demonstrate in exploratory analysis that CLaN-A modulates parietal ICNs. This relationship suggests parietal targets in further investigations of the neural determinants of automaticity in synaesthetic concurrents. These investigations highlight the requirement for complete and accurate descriptions of phenomenology in the investigation of the synaesthetic experience.

6.2 Conclusions

Synaesthesia provides a unique opportunity to study altered conscious states in a population who are on the whole free from significant clinical disorders. As such, investigations of this trait may help to determine the necessary and sufficient neural processing required in the generation of a conscious experience. Throughout this thesis we have conducted investigations of synaesthesia with significant weight afforded to the first-person phenomenological account of the experience and the individual difference measures which may be obtained on this basis. In so doing we have illustrated that synaesthetes are not a homogeneous group and demonstrated that population level inferences made from group data may mask informative effects.

In synaesthetic colour processing, we demonstrate that activation in colour selective areas is dependent on individual differences in phenomenology, specifically the localisation and automaticity of synaesthetic concurrents, and we are thereby able to reconcile previous attempts to replicate this key finding in the GCS literature. Both context specific FC and rsFC suggest that increased localisation of concurrents is supported by visual networks, particularly interactions between the cuneus and lateral visual areas. We found no evidence for connectivity between parietal and colour areas in either of our FC analyses, supporting the hypothesis of Terhune et al. (2011) that GCS is the result of alterations in low level visual processing. Our exploratory analysis regarding the impact of automaticity in concurrents suggests this feature to be an informative tool for future assessment

of breakthrough of synaesthetic concurrents into conscious experience, particularly implicating integration of a distributed network of areas with parietal activity. We suggest that future investigations of this trait make use of the significant advantage afforded in recognising the impact of individual difference effects, and propose a move towards further exploration of qualitative data collection to obtain detailed first-person phenomenological accounts of the experience.

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Appendix A

Spatial-form-synaesthesia: Interview themes

A.1 Html expandable mind map

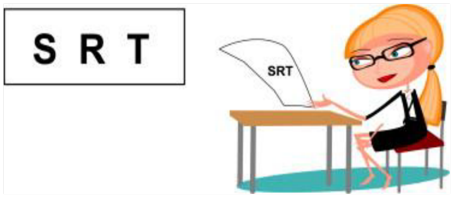
Online supplementary material contains the full description of all themes uncovered during EI with this subject. Each theme can be explored by clicking the expand (+) button, revealing a summary description and further sub-themes. The bottom-most level contains verbatim excerpts from the in EI sessions, along with a interview date and paragraph reference. To access these results, go to:
https://sites.google.com/site/cassandragould/thesis_sfsphenomenology

Appendix B

Grapheme-colour synaesthesia phenomenology questionnaires

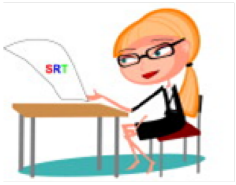
ILLUSTRATED SYNAESTHETIC EXPERIENCE QUESTIONNAIRE

Please fill in the following as accurately as possible. This information is extremely valuable to this study.
You may go back and change your answers at any time.



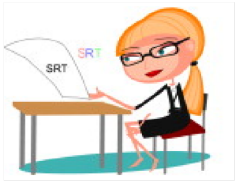
Imagine that you are the lady in this illustration. Whilst you are viewing the letters "S R T" printed in the box, please rate how closely the illustrations below represent your experience (one being the least accurate, seven being the most accurate).

Least accurate Most accurate



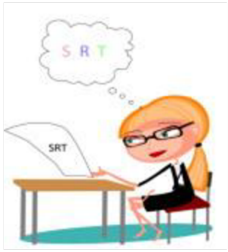
1 ☐ ☐ ☐ ☐ ☐ ☐ ☐ 7

- You see a specific colour
- The colour has the same shape as the letter or number
- The colour looks like it is on the page



1 ☐ ☐ ☐ ☐ ☐ ☐ ☐ 7

- You see a specific colour
- The colour has the same shape as the letter or number
- The colour is not on the page, but floating in space



1 ☐ ☐ ☐ ☐ ☐ ☐ ☐ 7

- You experience a coloured copy of the letters in your 'minds eye' and black and white on the page

1 ☐ ☐ ☐ ☐ ☐ ☐ ☐ 7

- You experience a block of colour in your 'minds eye' and black and white on the page

1 ☐ ☐ ☐ ☐ ☐ ☐ ☐ 7

- You experience a sensation of knowing a letters colour

Figure B.1: Illustrated Synaesthesia Experience Questionnaire (ISEQ) (Skelton et al., 2009).

ROUW AND SCHOLTE (2007) PA QUESTIONNAIRE

Please indicate to what degree these statements correspond with your synesthetic experiences (1= strongly disagree, 5= strongly agree).

1. When I look at a certain letter or number, I **see** a particular colour.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

2. When I look at a certain letter/number, the accompanying colour appears only in my thoughts and not somewhere outside my head (such as on the paper).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

3. When I look at a certain letter/number, the accompanying synesthetic colour comes in my thoughts but on the paper appears only the colour in which the letter/number is printed (e.g. a black letter against a white background).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

4. It seems that the colour is on the paper where the letter/number is printed.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

5. The figure itself has no colour but I am aware that it is associated with a specific colour.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

6. The colour is, if it were, projected onto the letter/number.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

7. I do not see letters/numbers literally in a colour but have a strong feeling that I know what colour belongs to a certain letter/number.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

8. The colour is not on the paper but floats in space.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

9. The colour has the same shape as the letter/number.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

10. I see the colour of a letter/number only in my head.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

11. I see the synesthetic colour very clearly in proximity of the stimulus (e.g. on top of it or behind it or above it).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

12. When I look at a certain letter/number, the synesthetic colour appears somewhere outside my head (such as on the paper).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

Figure B.2: Rouw and Scholte Projector-Associator questionnaire (RS-PA) (Rouw & Scholte, 2007).

COLOURED LETTERS AND NUMBERS QUESTIONNAIRE

Please indicate to what degree these statements correspond with your synesthetic experiences (1= strongly disagree, 5= strongly agree).

1. I experience the synaesthetic colours even if I do not attend to them specifically (e.g., while reading a book)

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

2. I see the synaesthetic colours on the computer screen (or very close to it).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

3. It feels like I have to go and fetch the colours, rather than the colours coming to me.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

4. I experience the synaesthetic colours in several locations at the same time (for instance, both on the screen and literally inside my head or some other combination).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

5. I only experience the synaesthetic colours of letters/numbers if I think about them as having a colour.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

6. When I am looking quickly at a page of a book the synaesthetic colours appear before I am aware of what the letters/words are.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

7. I do not ''see'' colours when I look at the letters/numbers.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

8. It seems that the colour is on the screen where the letter/number is printed.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

9. The synaesthetic colours appear automatically without any effort on my part.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

10. I can point to the location of the synaesthetic colours.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

11. My synaesthetic colours did not change their intensity over the years.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

12. I use my synaesthetic colours deliberately for remembering sequences of numbers (e.g., PINs, telephone numbers).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

13. I deliberately try to use my synaesthetic colours in my everyday life.

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

14. I use my synaesthetic colours to remember dates and plan appointments (e.g., 28.02.2010).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

15. My synaesthetic colours were weaker in the past (i.e., years ago).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

16. My synaesthetic colours were stronger in the past (i.e., years ago).

1: ☐ 2: ☐ 3: ☐ 4: ☐ 5: ☐

Figure B.3: Coloured letters and numbers questionnaire (Rothen, Tsakanikos, et al., 2013).

Table B.1: Locations of colour selective ROIs in synaesthetes and controls. Coordinates in MNI space.

Group	Participant number	Left colour area	Right colour area
Control	10151	[-2,-100,2]	[8,-90,8]
	10208	[-42,-86,8]	[2,-84,0]
	10330	[0,-88,-12]	[0,-88,-12]
	10355	[-22,-58,-14]	[4,-86,-12]
	10374	[-6,-98,-4]	[36,-50,-18]
	10400	[-20,-88,-16]	[8,-86,-8]
	10418	[-28,-56,-16]	[28,-56,-16]
	10472	[-36,-56,-14]	[26,-78,-20]
	10523	[-30,-88,2]	[16,-92,-4]
	10584	[-40,-88,18]	[36,-54,-18]
	10710	[-6,-96,12]	[4,-94,8]
	10737	[-30,-78,-20]	[16,-92,-10]
	10738	[-28,-82,-18]	[8,-86,6]
	10755	[-40,-62,-18]	[32,-94,14]
	10795	[-26,-84,16]	[2,-94,8]
	10806	[-44,-50,-12]	[14,-76,-14]
	10816	[-30,-96,18]	[26,-92,20]
	10821	[-2,-88,2]	[2,-84,4]
	10887	n/a	n/a]
	10899	[-38,-80,8]	[12,-100,16]
Synaesthete	151	[-30,-60,-16]	[30,-72,-18]
	208	[-28,-84,-24]	[32,-70,-20]
	330	[-36,-84,-18]	[28,-72,-16]
	355	[-40,-68,-20]	[24,-94,26]
	374	[-6,-100,-4]	[6,-92,12]
	400	[-24,-76,-20]	[8,-90,-12]
	418	[-32,-84,-12]	[14,-102,2]
	472	[-34,-90,20]	[12,-98,10]
	523	[-14,-100,-6]	[36,-74,-18]
	584	[-22,-80,-14]	[16,-98,12]
	710	[-10,-98,8]	[32,-48,-10]
	737	[-30,-72,-16]	[20,-98,6]
	738	[-18,-86,-18]	[14,-94,2]
	755	[-8,-82,-14]	[10,-100,12]
	795	[-36,-84,12]	[36,-82,26]
	806	[-4,-94,-8]	[30,-52,-16]
	816	[-34,-72,-14]	[34,-56,-12]
	821	[-10,-100,-6]	[34,-72,-20]
	887	[-38,-52,-10]	[38,-52,-10]
	899	[0,-96,-8]	[18,-94,-12]

Appendix C

Resting state functional network connectivity results

Table C.1: FWE corrected significant clusters and peaks in resting state networks from collapsed group results. 2nd level maps thresholded at $p(Unc.peak) < .001, k = 10$. Significant peaks and clusters reported at $p(FWE) < .005$. (Continued in table C.2).

Network & area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
Medial visual							
Fusiform_L	<.001	28378	<.001	7.842	-28	-74	-14
Cerebelum_Crus1_L			<.001	7.830	-46	-66	-22
Cerebelum_Crus1_R			<.001	7.775	48	-70	-20
Frontal_Sup_Medial_L	<.001	1013	<.001	6.210	-2	62	32
Frontal_Sup_Medial_R			.001	5.711	6	70	4
Temporal_Pole_Sup_R	<.001	1207	.008	5.379	54	18	-12
Temporal_Pole_Sup_R			.023	5.192	50	22	-20
Frontal_Med_Orb_R			.025	5.176	4	66	-6
Supp_Motor_Area_R	<.001	465	.092	4.873	6	14	46
Precentral_R	<.001	1277	.151	4.746	48	8	36
Frontal_Sup_R	.005	299	.890	4.054	16	34	50
Frontal_Mid_L	<.001	489	.938	3.986	-30	54	26
Lateral visual							
Lingual_R	<.001	18708	<.001	Inf	14	-54	2
Cingulum_Ant_R	<.001	452	.314	4.542	8	38	26
Precentral_L	.042	205	.456	4.417	-36	-12	44
Temporal_Sup_R	.010	264	.843	4.110	62	-4	0
Striate and polar visual							
Cuneus_R			<.001	7.804	12	-100	6
Calcarine_L			<.001	7.726	2	-88	-4
SupraMarginal_R	<.001	734	.001	5.844	56	-36	40
Vermis_1_2	.001	365	.011	5.320	4	-42	-24
Temporal_Pole_Sup_L	.025	226	.106	4.839	-36	22	-28
Frontal_Sup_Medial_L	.036	211	.751	4.191	2	32	62
SupraMarginal_L	.006	288	.782	4.165	-60	-26	38
Auditory							
Rolandic_Oper_R			<.001	7.791	58	-20	14
Rolandic_Oper_L			<.001	7.689	-62	-6	10
Rolandic_Oper_L			<.001	7.464	-62	2	2
Supp_Motor_Area_L	<.001	1339	.001	5.757	0	-10	60
Supp_Motor_Area_R			.019	5.223	2	-4	46
Postcentral_L	<.001	545	.033	5.116	-20	-42	82
Cerebelum_9_L	.085	177	.044	5.051	-4	-44	-34
Cingulum_Mid_R	<.001	1041	.074	4.927	8	-28	34
Frontal_Mid_R	<.001	449	.089	4.882	48	44	20
Sensory Motor							
Paracentral_Lobule_L			<.001	7.779	0	-24	64
Supp_Motor_Area_R			<.001	7.692	2	-20	74
Frontal_Mid_Orb_R	<.001	1196	.022	5.197	44	54	-8
Frontal_Inf_Orb_L	<.001	433	.223	4.641	-46	48	-12
Hippocampus_R	.015	248	.252	4.607	36	-42	4
Occipital_Sup_R	<.001	510	.486	4.392	20	-74	30
ParaHippocampal_L	.002	339	.530	4.358	-20	-8	-32
Cerebelum_Crus2_L	<.001	659	.580	4.321	-16	-84	-34
Vermis_1_2	.008	278	.640	4.276	2	-28	-18
Thalamus_L	.001	361	.757	4.185	0	-14	14
Lingual_R	.007	280	.761	4.182	8	-38	2
Rectus_L	.005	299	.915	4.024	0	54	-16

Table C.2: (Continued from table C.1) FWE corrected significant clusters and peaks in resting state networks from collapsed group results. Thresholded at $p(Unc.peak) < .005), k = 10$. (Continued in table C.3).

Network & area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
Tempro-parietal							
Precuneus_R	<.001	4151	<.001	7.374	2	-60	48
Temporal_Mid_R			<.001	7.203	58	-42	8
Temporal_Mid_L			<.001	7.125	-62	-56	12
Temporal_Mid_L			<.001	7.114	-60	-44	6
Temporal_Mid_R			<.001	7.036	54	-38	-2
Precuneus_L			<.001	6.739	-8	-54	50
Precuneus_R			<.001	6.641	2	-54	64
Frontal_Inf_Orb_R	<.001	1781	<.001	6.039	52	30	-12
Frontal_Inf_Orb_R			.003	5.577	52	24	-4
Cerebelum_Crus2_L	<.001	521	.005	5.459	-22	-82	-44
Frontal_Mid_R			.012	5.311	48	10	52
Thalamus_R	<.001	1424	.042	5.055	10	-30	0
Lingual_R			.048	5.024	10	-40	0
Cerebelum_Crus2_R	<.001	573	.231	4.628	22	-80	-44
Medial parietal							
Cerebelum_Crus1_R	<.001	1054	<.001	5.971	48	-66	-26
Cerebelum_8_L	.927	66	.035	5.097	-30	-38	-50
Rolandic_Oper_R	.001	409	.123	4.799	66	-2	8
Supp_Motor_Area_R	.006	289	.200	4.671	2	2	78
Cerebelum_Crus1_L	<.001	1105	.256	4.600	-50	-68	-30
Olfactory_L	<.001	462	.479	4.396	0	24	-4
Cerebelum_Crus2_L	.013	256	.503	4.378	-2	-80	-32
Hippocampus_R	.001	387	.716	4.216	10	-10	-14
Temporal_Sup_L	.001	368	.985	3.859	-62	4	-2
Left frontoparietal							
Temporal_Inf_R	<.001	1074	<.001	7.238	62	-46	-14
Angular_R	<.001	3569	<.001	7.233	40	-58	48
Parietal_Sup_R			<.001	7.165	34	-72	48
Frontal_Inf_Tri_R	<.001	3286	<.001	6.527	52	32	20
Cerebelum_Crus2_R	<.001	2377	<.001	6.462	10	-80	-40
Frontal_Inf_Tri_R			<.001	6.424	50	40	12
Frontal_Mid_R			<.001	6.331	42	58	6
Cerebelum_Crus2_R			<.001	6.255	12	-74	-34
Cingulum_Mid_L	<.001	1492	<.001	6.220	-2	-36	34
Occipital_Sup_R			<.001	6.191	26	-72	44
Cerebelum_Crus1_R			<.001	6.067	32	-68	-36
Temporal_Inf_R			.006	5.425	62	-28	-22
Postcentral_R	<.001	635	.336	4.507	12	-30	82
Right frontoparietal							
Cerebelum_Crus2_L	<.001	2309	.001	5.807	-40	-72	-46
Parietal_Inf_L	<.001	583	.004	5.494	-42	-60	52
Cerebelum_Crus2_L			.036	5.087	-10	-82	-32
ParaHippocampal_R	<.001	614	.090	4.874	8	-8	-22

Table C.3: (Continued from table C.2) FWE corrected significant clusters and peaks in resting state networks from collapsed group results. Thresholded at $p(Unc.peak) < .005), k = 10$.

Network & area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
Executive control							
Temporal_Pole_Sup_L	<.001	22009	<.001	7.373	-50	14	-6
Insula_R			<.001	6.959	40	20	-2
Cingulum_Ant_L			<.001	6.756	0	42	12
Cingulum_Mid_L	<.001	3727	.002	5.623	-14	-42	50
Precuneus_L			.011	5.323	-4	-56	66
Precuneus_R			.016	5.254	4	-52	58
Cerebelum_Crus1_L	<.001	501	.669	4.250	-46	-62	-28
SupraMarginal_L	.011	266	.911	4.026	-64	-36	30
Default mode							
Frontal_Sup_Medial_R			<.001	7.703	10	66	4
Angular_L	<.001	2263	<.001	7.361	-44	-70	34
Angular_L			<.001	7.017	-44	-72	42
Angular_R	<.001	1707	<.001	6.669	52	-62	34
Frontal_Sup_R	<.001	1721	<.001	6.628	22	30	50
Temporal_Pole_Sup_L	<.001	729	<.001	6.467	-34	18	-28
Angular_R			<.001	6.384	46	-68	36
Temporal_Mid_L	<.001	1023	<.001	6.254	-64	-14	-18
Angular_L			<.001	6.244	-52	-66	28
Frontal_Sup_R			<.001	5.991	26	22	52
Postcentral_L	.002	334	.001	5.789	-54	-8	24
Temporal_Mid_L			.004	5.527	-64	-22	-12
Frontal_Mid_R			.005	5.477	38	20	48
Postcentral_R	<.001	1664	.011	5.335	16	-38	84
Cerebelum_3_R	<.001	414	.016	5.263	20	-24	-26
Temporal_Mid_R	<.001	871	.038	5.083	62	-12	-16
Precentral_R			.040	5.067	50	-16	46
ParaHippocampal_L	<.001	446	.062	4.968	-20	-22	-26
Cerebelum_Crus1_L	.006	290	.105	4.837	-24	-90	-22
Cerebelum_Crus2_L	.009	273	.214	4.650	-40	-74	-44
Paracentral_Lobule_L	<.001	481	.504	4.375	-14	-24	80
Cerebelum_Crus2_R	<.001	1184	.613	4.293	40	-72	-46
Temporal_Pole_Mid_R	.002	340	.900	4.040	48	18	-38

Table C.4: FWE corrected significant clusters and peaks in additional resting state networks identified in synaesthetes. Thresholded at $p(Unc.peak) < .005), k = 10$.

Network & area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
Supplementary motor area							
Supp_Motor_Area_R	<.001	2359	<.001	6.449	8	8	72
Calcarine_L	<.001	742	.501	4.537	4	-94	6
Postcentral_L	<.001	348	.551	4.498	-24	-36	40
Cerebelum_6_L	.033	173	.943	4.128	-32	-32	-32
Frontal_Mid_R	.032	174	1.000	3.649	32	40	20
Supp_Motor_Area_R	<.001	2359	<.001	6.449	8	8	72
Medial visual							
Calcarine_L	<.001	3378	.005	5.471	-2	-90	-6
Temporal_Sup_R	<.001	736	.009	5.356	44	-28	14
Temporal_Sup_L	<.001	1388	.301	4.691	-60	-32	14
Frontal_Mid_R	.002	268	.557	4.498	36	60	4
Hippocampus_R	.002	271	.944	4.130	26	-38	8
Angular_R	.001	305	.972	4.063	40	-72	48
Cerebelum_9_R	.004	243	.997	3.914	0	-44	-44
Parietal_Sup_L	.011	206	.999	3.865	-30	-66	50
Calcarine_L	<.001	3378	.005	5.471	-2	-90	-6
Calcarine_L			.042	5.080	-8	-96	-10
Temporal_Sup_R	<.001	736	.009	5.356	44	-28	14
Left frontoparietal							
Parietal_Sup_L	<.001	12557	<.001	6.262	-22	-74	58
Temporal_Inf_R	<.001	388	.073	4.973	60	-56	-14
Temporal_Inf_L	<.001	749	.106	4.899	-58	-64	-10
Frontal_Sup_R	<.001	495	.806	4.290	28	2	66
Parietal_Sup_L	<.001	12557	<.001	6.262	-22	-74	58
Frontal_Sup_L			<.001	6.093	-26	4	66
Parietal_Sup_L			<.001	5.943	-32	-50	66